ANNUAL REVIEW OF PHYSIOLOGY

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ANNUAL REVIEW OF PHYSIOLOGY

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PREFACE

In presenting this second volume of the *Annual Review of Physiology* to our colleagues in the sciences, we find it appropriate in the introductory pages to mention several matters that have been before us in the past few months.

The first thought is, in some respects, a disturbing one for it has its origin in the turbulent conditions that exist abroad. This is not the place to discuss the sufferings of the war which affect everyone, in some measure at least, however distant he may be from the areas of conflict. But there is something in the stress of the times that draws us close to our colleagues the world over, something which makes us very acutely aware of the fraternal bond of goodwill that unites us to our fellow scientists in all places.

The stern exigencies of war render difficult the pursuit of fundamental research and even more trying, doubtless, the preparation of original papers and reviews. With this in mind we consider it fitting to express the deep sense of gratitude that we feel to a number of our colleagues abroad who have accepted invitations to participate in the authorship of the forthcoming volume and to others who have assisted us most generously in matters that pertain to the present one.

The reviews in the volume that we now introduce were all written, as it happens, in this country and in Canada. We know something of the effort that has been expended in their preparation, and we are not unaware of the difficulties of the task. We suspect that there is no one who feels that he overcame, to his complete satisfaction, the troublesome problems that constantly harass the authors of these reviews—the rigorous necessity of confining a review to the space assigned, the selection of the papers to be reviewed, the desire to be exhaustive in treatment and yet to be critical—these and many other problems have combined to make the task an arduous one. The appreciation that we wish to express to the writers of these reviews, while conveyed by us, comes ultimately from the readers of the Review, of whom many have expressed the sentiments that we now record.

Several who have been good enough to write to us on matters pertinent to the Review have questioned the advisability of using,

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as we have done, the two or three different forms of literature citation to be found within these volumes. Perhaps we have erred in extending to authors the privilege of using either of two recommended systems—the alphabetical or the numerical method of collecting references. We propose in future volumes to recommend a combination of the two systems—an alphabetical, but numbered bibliography which will permit references to be made by number in the text, but which will also facilitate the location of papers in the bibliography. However, we trust that our readers will be patient with us if there are occasional lapses from grace. There are those among us who, in the preparation of articles for press, are convinced of the superiority of our own method of literature citation over any other recommended system; there are others who feel driven to rebel at any suggestion of complete uniformity. Perhaps, after all, the question is of minor importance and it may be that the eccentricities of genius should be recognized by granting a reasonable measure of latitude in matters of this sort

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DEVELOPMENTAL PHYSIOLOGY

By H. W. Mossman

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There is no sharp line setting off the period of development of an organism from its period of maturity, nor is there even a stage at which we can definitely say that development begins, for we know that life among multicellular organisms is a continuous stream from generation to generation. It is certain then that any limits one sets on what one shall consider as embryonic development are purely arbitrary and moreover must vary in accordance with the type of organism under discussion.

The outline for this review follows roughly the ontogenetic schedule, starting with fertilization and ending with the problems connected with final metamorphosis to a physiological state approaching that of the adult. To make such an outline readily applicable for review the terminology customarily employed in the various fields has been used. Some overlapping and certain illogical groupings necessarily occur in attempting to pigeon-hole the components of as broad a science as developmental physiology. Due to lack of space, some of the subjects are merely indicated by name and a few pertinent references cited. Some of the direct quotations are from author's abstracts.

Initiation of Development in the Egg

The general subject has been recently reviewed by Just.

Fertilization.—There has been but little work during the past few years which has added anything fundamentally new to our understanding of the physiology of the process of fertilization itself. One should cite, however, recent papers by Frank and by Morgan.

In recent years much work has been done on the physiology and the biochemistry of sperm and semen, due largely to the stimulus resulting from the need of perfecting the technic of artificial insemination in domestic animals and of contraception in man. It is possible that the mass of information accumulated in these studies will eventually prove of value in elucidating the physiology of the fertilization process. For recent contributions in this field, see McKenzie *et al.*

Parthenogenesis.—Studies on artificial parthenogenesis have contributed to our knowledge of the fertilization process in two ways: (1) They have shown what sorts of stimuli substituted for sperm penetration will initiate development. (2) They have helped demonstrate that the sperm chromatin is of importance, not only in the hereditary traits which it carries, but also in giving vigor to the early embryo, apparently by increasing the total amount of nuclear material. Embryos produced by artificial parthenogenesis are often abnormal and are usually weak and slow to develop, whereas embryos produced by natural parthenogenesis where the chromatin amount, though not necessarily the chromosome number, is kept normal, are vigorous.

A start toward an understanding of the differences in the physiological processes of artificially stimulated eggs and normally fertilized ones has been made by Brachet (1) and by Tyler & Horowitz in papers [reviewed by Needham (3)] which compare their respiratory rates. The oxygen consumption of the egg was reduced in the same proportions by both normal fertilization and artificial activation, but after this initial similarity the oxygen consumption of the normal embryos increased much faster than that of the parthenogenetic ones, whether or not the latter were undergoing differentiation with or without cleavage. Laser & Rothschild report similar results on fertilized *Psammechinus* ova. Pincus (2) has compared artificially activated and normally fertilized rabbit eggs both *in vitro* and in the uterus. Some of the interesting things shown are that "the initiation of activation is an all-or-none process, though its continuation probably is not"; that haploid, diploid and tetraploid parthenogenesis can be produced; that foreign sperm may activate to a limited degree even without penetration of the zona pellucida; and that "living young may arise from artificially activated eggs, but only in a limited number of cases." Reimann & Miller believe they have induced parthenogenetic activities in one human ovum.

Differentiation

Cellular physiology.—Important contributions have been made in the following fields: (1) mitosis and cell division (Chambers; Marsland); (2) cell potencies and intracellular segregation (Beams & King; King & Beams; Costello; Pease).

Organization and developmental capacities.—Mention should be

made of studies of segregation at cleavage and gastrulation by Novikoff, and of polarity and axial gradients by Hörstadius, by Hall, by Hamburger and by Swett.

The problems of embryonic "induction" have long occupied the center of the stage of experimental embryology. They pertain to the general question of how the orderly differentiation of an embryo is controlled. The experimental results have given us an enormous mass of information as to the morphogenetic interrelations of embryonic parts, on which has been built an unusually interesting and valuable but involved set of theories and concepts. Unfortunately these theories and concepts are commonly expressed in an ambiguous, ill-defined and semi-philosophical terminology. When we realize that from all these researches there have come only a very few real physiological facts, we can understand the confusion of ideas that exists. Peculiarly enough, in all of this so-called "developmental mechanics," instances where "mechanical" factors are of importance are scarce, and progress toward a real understanding of the phenomena in terms of tangible physiological concepts has had to wait for the perfection of methods by which the biochemist can attack the problem. The morphogenetic facts and theories are serving the chemist and physiologist as a chart by which they can plan their attack on the functional basis of the morphogenetic phenomena.

In spite of the complexity of the problems and the amount of research being done on induction, it is not essential to spend much time on them here, because they have been so adequately covered recently by others. For an excellent relatively simplified outline of the whole field, one should consult Needham (2). Spemann's book gives a complete presentation of the experimental morphogenetic side of development; Weiss presents about the same material from a somewhat different point of view; and Needham's "Chemical Embryology" together with his review in the first volume of the Annual Review of Physiology brings the physiological side practically up to date.

Dealing with the problem of evocation and individuation, one must cite a recent paper by Brachet (2) dealing with protein and carbohydrate metabolism in the frog egg. He found little sign of variation in protein metabolism during development from segmentation to neurulation. There was, however, a marked increase in phosphorus output. The dorsal halves (organized areas) had a

very much higher oxygen consumption rate than the ventral. His experiments also indicated that glucoside metabolism has little morphogenetic importance. Waddington suggests "that the reason why the organization center is the only region of the living gastrula which is capable of evocation is because it has a particular metabolism which 'liberates' the evocator from some combined or masked form." He cites the fact of the known peculiarities of metabolism in the organizer center and suggests as a working hypothesis that the action of both natural and artificial evocators is due "to their ability to cause normal ectoderm to adopt the type of metabolism crucially characteristic of the organizer."

Jacobson using microchemical methods has shown that "epiblast cells lose much of their glycogen when invaginating through the streak or node to form the mesoderm or head process, both of which are poor in glycogen." On the other hand, he says that "when invaginating, the epiblast cells show an increase of lipoids (probably sterols), which again decrease in the mesoderm cells but are retained by the cells which form the head process." He summarizes as follows:

> The higher lipoid content is correlated: 1. with the organizing effect of the primitive streak, node and head process; the head process loses its higher lipoid content and its organizing power simultaneously, i. e., when it differentiates into a notochord; 2. with the behavior of Nile-blue sulphate marks, which in the chick is governed by the lipoid metabolism of the streak, node and head process; when a mark reaches one of these structures it is there retained and no longer follows the movements of the cells. This is a source of error in experiments with such marks.

Plants, of course, exhibit many of the same developmental phenomena as animals. In them polarity, axial arrangements and gradients are particularly obvious. Whitaker in a series of papers (only two of which have been included in the bibliography) has studied the physiological background of polarity in the egg of *Fucus* in which the position of the initial rhizoid protuberance determines the polarity of the whole embryo. He has been able to induce rhizoid formation in a particular region by local application of hydrogen ions in suitable concentrations. Directed white light causes the rhizoid to form on the opposite side. When the eggs are enclosed in small tubes, the rhizoids tend to form on the side where the concentration of substances diffusing from the egg is greatest. Temperature gradients across the egg result in rhizoid formation on the warm side. In 93 to 99 per cent of centrifuged eggs retaining

visible stratification the rhizoids formed within 10° of the centrifugal pole, even though the eggs had been embedded in random positions in firm seawater-agar before centrifuging. Finally, directed light or pH may alter or completely reverse the polarity imposed by centrifugalization. It is possible to cause these normally spherical eggs to assume an elongate shape, and if this is done, the rhizoid forms at one end; but even this can be reversed causing protuberance from near the end of the short axis toward the bottom of the dish by increasing the acidity to pH 6.0 [Whitaker (2)].

In connection with the subject of gradients one should also mention the experiments of Wolff (2) who has perfected a technic for destroying localized areas of embryos by x-ray irradiation and observing the effect on the further development and organization of the whole. Even with destruction of the entire head, the chick embryo body may develop quite normally, showing that in these cases determination is strong enough to carry on in spite of what must be an extreme interference with the general axial gradient system as well as with the organ systems themselves.

There seems to be little to report on the physiology of competence. There are of course numerous papers dealing with the morphogenetic aspects of the problem. One of the more recent of these is by Oppenheimer who has made a number of interesting observations on the potencies of the germ ring in Teleosts.

The relations of the endocrine glands and hormones of Amphibia to growth and metamorphosis are too well known and too completely tied up with the field of endocrinology to be reviewed here. Insect metamorphosis, however, promises to be another fertile field for study of similar physiological processes. The hormonal influence of the corpus allatum and ring gland on pupation is already well established [Hadorn & Neel, and Becher & Plagge]. Bodenstein has studied the differentiation of the pupa into the imago and has shown that there again the head region influences, apparently by hormones, the rest of the organism.

In the numerous recent papers on the developmental capacities of later tissues and organs, there is no real physiological analysis of the mechanism by which isolated tissues or organs are able to maintain more or less their normal course of differentiation, because so far no one has conceived a method of attack on this difficult problem. The aim is usually to establish the time at which

tissues or organs become "self-differentiating" in any particular case, and to describe the often bizarre anatomy of the differentiated organs. Such studies as those of Adelmann on somite substitutions have considerable value in tempering the morphologists' interpretation of ontogenetical processes, and may eventually give clues to the physiological processes underlying such phenomena.

Intrinsic versus extrinsic factors.—Reference should be made to studies of pigmentation and feather and hair structure by Rawles, by Reed, and by Reed & Alley; of sex determination by Willier, by Green *et al.* by Turner, by Burns, by Wolff (1), by Dantschnakoff, by Puckett, by Foote & Witschi, and by Herbst.

Probably the most instructive recent attempts to analyze the developmental potencies of tissues and organs have been made on bone and cartilage. For a review of the earlier work on this subject consult Murray. Fell investigated the development *in vitro* of the sternal rudiment of the budgerigar (parakeet) and showed that the development of the cartilaginous sternum is largely controlled by intrinsic factors. Whole sterna develop keels in the absence of pectoral muscles and half sterna even develop half keels. Thus neither muscular tension nor growth pressure of the two halves against one another is a factor in the initial formation of the keel. The concavity of the deep side of the sternum also develops in the absence of viscera and regardless of whether the rudiment is cultured with ventral or dorsal side up. The posterior lateral processes also form. That extrinsic factors are important in providing optimal conditions for expression of inherent potentialities seems likely from the fact that the half-keel which develops *in vitro* from a single isolated plate is not vertical but acquires a secondary bend, suggesting that union of the two sternal plates may be a factor in producing the normal straight keel.

Glücksmann (1) has shown that pressure is a definite factor in the orientation of bone spicules *in vitro* and in another paper (2) concludes that, although pressure is not an essential factor in cartilage formation, yet when it is applied to periosteum or perichondrium it seems to initiate chondrogenesis mechanically, and in some as yet unknown way seems to establish conditions which lead to the formation of ground substance.

Glasstone demonstrated that the molar tooth germs of the rat and rabbit have remarkable powers of self-differentiation when cultivated *in vitro*. Even if transplanted before cusp formation,

they form cusps during cultivation which are "almost normal in shape, number and arrangement." Odontoblasts and dentine, and ameloblasts and enamel differentiate *in vitro*.

The skeleton of Echinoderms has been utilized by Ubisch in studying these problems. He concludes that protoplasmic viscosity is highly important in determining the type of skeleton in these creatures and interprets the variations found in hybrids and chimeras on this basis. Apparently the viscosity of the protoplasm is more closely related to genic control than the skeletal parts themselves, the latter being a secondary result of the nature of the protoplasm.

All this work has tended to show that skeletal and organ morphology is perhaps a bit more dependent on inherent or genic factors than might have been supposed, but it leaves us almost as far as ever from any physiological explanation of the correlated differentiation of the organs and tissues of the body. More has been done to elucidate the physiology of bone deposition by the biochemical approach, but this is too far removed from embryology to warrant discussion here.

Experiments on Early Mammalian Embryos

While the physiological problems of development of mammalian eggs are without doubt fundamentally similar to those of other forms, the great difference both in the type of egg and in its normal environment and therefore in the technics necessary for its study makes it simpler to consider these experiments separately. Then, too, the point of view and purpose of those working on mammalian material usually differs widely from that of those working on lower forms. Aside from studies on presumptive potencies of various regions of the germ disc there has been little tendency to repeat work done on non-mammals. On the contrary most of the work has been definitely physiological or biochemical in viewpoint. The rise of the endocrinology of mammalian reproductive physiology has influenced the outlook of many of these investigators. Pincus (1) presents perhaps the most important collection of information on the whole subject, but no attempt will be made to review here the material already set forth by him. Only a few recent papers will be mentioned.

Delayed fertilization.—Blandau & Young found that, as fertilization was delayed in guinea pigs, the number of sterile insemina-

tions and of abnormal pregnancies terminated by embryo death and abortion increased, while litter size and normal pregnancies decreased. The first effects of delay were apparent in animals inseminated eight hours after ovulation, while after twenty hours no normal development occurred and after thirty-two hours no development at all. They demonstrated that these effects are due to egg age at fertilization, not to faulty or delayed implantation. The physiological cause of this abnormal development after late fertilization is unknown.

Effect of hormones.—Pincus & Werthessen have studied the effects of estrone, progesterone, ascorbic acid and glutathione on rabbit blastocysts in the uteri of ovariectomized females and *in vitro*. Their conclusions are quoted:

> When progesterone is injected in varying doses into such females ovum growth and glandular proliferation are closely correlated. Oestrone injected in combination with progesterone inhibits ovum growth in low dosages and glandular proliferation in higher dosages. Ascorbic acid injected alone (in the dosages employed) has no detectable effect upon either ovum growth or glandular proliferation but in combination with progesterone it inhibits the former and does not affect the latter. Glutathione alone is also without effect, but in combination with progesterone both ovum size and glandular growth are increased. When ascorbic acid, glutathione and progesterone are injected together the ascorbic acid effect is overcome. It is concluded that glutathione can be made available for both ovum stimulation and pseudopregnant proliferation as the result of progesterone action and that ascorbic acid inhibits egg growth *in vivo* by shunting glutathione from the reactions leading to egg stimulation into reactions involving the reduction of ascorbic acid; oestrone presumably inhibits glutathione action by a similar shunting or by inhibition of the progesterone effect directly.

Brambell investigated the delaying effect of lactation on implantation and concluded that the delay is due not to an effect on the endometrium but to some "inhibitory effect on the blastocysts themselves, exerted otherwise than through lack of nutriment." He thinks it must be through a secretion of the endometrium. The work of Pincus & Werthessen quoted above may carry the answer to this question.

Culture and transplantation.—Nicholas has developed the culture of rat embryos *in vitro* to a point where they can be maintained in normal condition as long as ninety-six hours. He uses a circulating medium. Initial experiments show that the embryos withstand a wide range of pH (5.8 to 8.4), pressure, and temperature (70 to 110° F). Plasma cultures are not as effective.

Metabolism.—Boell & Nicholas have studied the respiratory metabolism of rat eggs and embryos by the Cartesian diver ultramicromanometer. Oxygen consumption averaged 0.00073 cmm. per egg per hour with no significant differences in the amount of respiration between one and eight cell stages. The respiration of isolated eight day embryos was approximately 0.01 cmm. per embryo per hour. During the next two days there was a twenty-fold increase in the amount of oxygen consumed, the increase paralleling the increase in embryonic mass.

Metabolism under the Special Conditions in the Embryo and Fetus

General metabolism.—Greig, Munro & Elliott have studied the metabolism of lactic and pyruvic acids in chick embryo tissue. Apparently embryo differs from most other tissues in that added glucose, lactate and pyruvate have little effect on respiration. Contrary to observations of Needham they find a large initial autoglycolysis. They conclude that in chick embryo and in some tumors the normal respiration does not depend upon the Krebs or the Szent-Györgyi system.

Hevesy, Levi & Rebbe have applied the method of introducing artificially radioactivated tracer compounds into the physiologic system of embryos. Radioactive sodium phosphate was injected into hens' eggs and the radioactivity of the phosphatide phosphorous from the yolk and embryo compared at various stages. That of the embryo was always highly active, but that of the yolk scarcely at all; therefore, they conclude that the phosphatide molecules of the embryo must have in the main been synthesized in the embryo instead of taken from the yolk directly. This and other data indicated that only the inorganic phosphorus present in the embryo is taken as such from the yolk or white. The papers of Atlas, and of Hammett should also be consulted.

Growth "hormones" and enzymes.—These have been studied by Davenport and by Kleinzeller & Werner.

Physiology of Specific Embryonic and Fetal Organs and Systems

Aside from the deductions made from morphological studies, the physiology of the fetus is even yet almost a virgin field. However, scientific books and discussions are full of assumptions, many

of them made so often that we are no longer conscious that they are mere assumptions, which leads one unacquainted with the situation to believe that there is little of importance left to learn about the matter. Cases in point are our common statements about the course of blood-flow through the fetal heart and the initiation of respiratory movements, both problems offering relatively simple experimental approaches, yet having only recently been subjected to any sort of critical physiological experimentation.

The physiology of the fetus can be approached by relatively minor modifications of the technic used in investigation of the adult. In view of the reasonably good conception which we now possess of adult physiology, it seems reasonable to believe that our best approach to the difficult and special problems of early development of the egg and embryo are from the top down, that is from adult down through fetal to embryonal physiology, rather than by direct attack on the earliest stages.

Barcroft and his associates have in the past few years advanced greatly our knowledge of the functioning of the fetal circulatory, respiratory and neuromuscular systems. Many of their experiments have necessarily been concerned with relatively elementary things such as the ratio between amount of blood in the placental and fetal circulatory systems, oxygen capacity of fetal hemoglobin, etc. Comparable things in adult physiology have been known for years.

Circulatory system.—Barcroft, Kennedy & Mason found that in the sheep the placentae (cotyledons) attain their maximum weight about mid-term when the fetus is the size of a large rat. The relation of total volume of fetal blood to fetal age varies considerably. The absolute amount of blood in the placenta is nearly constant during the last third of gestation although the fetus increases rapidly in size during this period. The percentage of cells to plasma during fetal life rises from about 43 at mid-term to 67 at term. Unexpected facts have been brought out in regard to total hemoglobin. A term fetus contains about 80 gms., but at eighty days it has only 4 gms. This manufacture of hemoglobin occurs chiefly after the one hundredth day, yet the only large fall in hemoglobin of the mother (about 50 gms.) takes place at about the fortieth day. McCarthy measured the colloidal osmotic pressures of the fetal and maternal sera of sheep, and showed that fetal

serum exerts a considerably higher pressure for a given concentration of protein and has a higher albumin content than maternal serum. Thompson & Pommerenke found that the mean total base values of maternal plasma and umbilical artery and vein plasma was around 146 milliequivalents with no differences greater than the range of experimental error. For tentative interpretations of the significance of some of these findings one should consult the paper of Barcroft *et al.*, just cited, and others from that laboratory.

The time of appearance and the nature of the first contractions of the heart have been studied by Goss using hanging drop cultures of whole rat embryos. In general his observations confirm the earlier ones made by Patten & Kramer on the chick and more recently by Copenhaver (1, 2) on *Amblystoma*, all of whom showed that the first portion to contract was the ventricle. Contractions in the rat appear at about 9 days 14 hours (three somite stage), long before circulation is possible because the arterio-venous connections are not patent. They are regular from the first with a rhythm of 37 to 42 per minute, and are confined to a small area (three to four cells) in the lateral ventricular myocardium of the left primitive heart tube. This area is near a constriction marking the junction of the primitive atrium and ventricle. The right tube begins contraction two hours later than the left. Its rhythm is regular, but independent of the left tube and slower by two to three contractions. The contractile activity gradually extends over the entire ventricular portion of each tube. It is then peristaltoid, extending from near the atrio-ventricular constriction toward the median region. The atrial region is still inactive. More and more of the median walls of each tube become active until the rhythm finally spreads across the mid-line and the right side assumes the rhythm of the left. All this has occurred before the circulatory circuit through the vessels is established.

Eyster, Krasno & Hettwer described the electrical potentials of the chick heart between the forty and seventy-two hour stages. They showed that the fundamental basis for the characteristic cardiac potentials and the electrocardiogram are acquired as early as are the properties of automaticity and contractility of the organ. Hoff *et al.* state that in chick embryos of about forty-eight hours the major features of the adult electrocardiogram have developed, yet at this time there is no nervous connection to the heart and no histologically distinguishable conduction tissue. Apparently,

as Eyster *et al.* pointed out, the electrical characteristics of the heart muscle are not only independent of the innervation and specialized conducting tissue, but also of the histological maturity of the muscle itself, since they occur long before it has assumed these features.

Copenhaver (2) demonstrated a remarkable degree of intrinsic control of pulsation rate by heteroplastic grafts of heart between *Amblystoma punctuatum* and *tigrinum*. The rate was always that of the donor, although the growth rate tended to approximate that of the host.

Barclay *et al.*, using x-ray cinematography on lambs delivered by Caesarian section, have shown that the foramen ovale remains patent after functional closure of the ductus arteriosus. The latest patency of the foramen observed was about six minutes after delivery, but they state that it may have remained open a considerable time after that. It was functionally closed in a lamb eight hours after normal birth. Most interesting of all are their direct observations on the muscular contractions of the valve of the foramen. They say that when the heart was open

> the foramen ovale was found completely closed by its valve, a delicate circular sheet of muscle about 1.2 cm. in diameter. When the upper margin of this sheet was gently touched with the tip of a seeker, it became detached for a short distance on either side of the point touched and a circular foramen about 0.6 cm. in diameter was produced as the musculature retracted. Although all pulsation had ceased in the ventricles, the superior vena cava was still contracting every fifteen to twenty sec. and just after each caval contraction the valves of the foramen ovale contracted upwards towards the point from which it had been detached, though the foramen was never completely closed by these post-mortem contractions.

Another line of evidence on the nature of the fetal circulation is provided by Barcroft, Kramer & Millikan. Tracings of the oxygen saturation of the carotid blood of lambs delivered by Caesarian section showed, among other things, that, when oxygen was administered from the start, 95 per cent saturation of the carotid blood could be reached within five minutes. They point out that this would not be expected if enough blood to be physiologically important was short-circuited through the foramen ovale.

Bauer (1, 2) compared the effect of asphyxia on the heart rate of the rabbit in late fetal and early neonatal life. Clamping the umbilical cord caused a fall (after an initial delay of forty to fifty seconds) which was not vagal. Vagal inhibition first appeared as

an increased reduction in heart rate in extreme asphyxia and was well developed by the eleventh postnatal day.

Respiratory system.—Rosenfeld & Snyder (1) showed that regular respiratory movements take place in rabbit fetuses *in utero*. They pointed out in a later note that this rhythmic breathing of amniotic liquor is probably a mechanism to assure distention of the alveoli and thinning of the septa before birth [Snyder & Rosenfeld (2)]. In a much more complete analysis of the problem [Snyder & Rosenfeld (1)], including observations on the cat, guinea pig and human fetuses as well as the rabbit, they say,

> Regulation of fetal respiration depends upon the oxygen and carbon dioxide level of fetal blood, but differs in certain respects from that of the adult. *a.* Oxygen want depresses or abolishes fetal respiratory movements. *b.* Carbon dioxide deficit results in depression or apnea of the fetus showing that a certain level of carbon dioxide is essential for the maintenance of fetal respiration. *c.* An excess of carbon dioxide has little or no effect. The depressant action of anoxemia is evidence that the carotid body mechanism is not functioning in the rabbit fetus before birth. The rate of respiration of a fetus varies according to the stage of development, being several times more rapid in postmature fetuses than in premature ones. The fetal respiratory system is peculiarly sensitive to narcosis. Respiratory movements may be abolished in the fetus at a level of analgesia which does not impair maternal respiration.

Rosenfeld & Snyder (2) describe two critical points in the transition between intrauterine and postnatal respiratory regulation: "1. the time of birth, when an abrupt change occurs to the adult type of response; 2. the beginning of the period of viability, when the capacity of the respiratory system to respond to excess carbon dioxide and low oxygen first becomes differentiated, although inhibited from functioning within the uterus."

Windle, Becker, Barth & Schulz made x-ray studies of fetuses of guinea-pigs *in utero* during the last half of gestation by means of the thorium dioxide technic. They found that thorium appeared in the fetal lungs only in cases of asphyxia. Obviously this is contrary to Snyder's belief that the fetal respiratory movements are normal. Barcroft's observations on the sheep may explain this seeming contradiction. In his review Barcroft (2) says,

> Summarising then the condition of knowledge at present, respiratory movement is a relic of the original mass movement from which other purposive movements are developed. The foetus of the sheep exhibits at 50 days a very highly respiratory rhythm which at that stage can be accelerated or deepened by consequent or somatic movement (exercise): up to this stage respiratory movement cannot be induced by asphyxia.

Respiratory movement and movement generally tends to disappear about the 50th to 60th day. The power is not lost however; it can be uncovered either by asphyxia or by section of the Central Nervous System above the medullary centres. This section can be made *intra-utero* without immediately affecting the growth of the foetus.

The type of respiration which is "uncovered" depends upon the position of the section; if below the red nucleus the respiration is of the gasping type and the muscular movements "jerky"; if above the red nucleus the respiratory movements are gradual as in normal respiration and the somatic movements sustained.

Neuromuscular system.—The possible influence of one part of the nervous system upon the development of another part is of interest. Detwiler using amphibia has shown that if the medulla is replaced by a segment of the spinal cord and the experimental animal connected to a parabiotic twin "nurse," the spinal cord below the medullary region is not retarded in growth. It seems that the medullary projection fibers, therefore, do not exert a trophic influence on the spinal cord.

The problem of nerve-muscle specificity has recently been investigated by Piatt in a series of forefoot regeneration experiments on an amphibian. He found a varying degree of specificity depending on the conditions of the experiment and concluded that there is no inherent attraction between a specific muscle and its normal nerve and that the degree of selective regeneration manifested by a nerve is probably dependent on extraneous factors, chiefly the nerve pattern itself. Hamburger using the transplantation technic on chick embryos also concluded that while there is evidence for some "attractive" force in the innervation of a limb, the nerves form a normal nerve pattern regardless of their origin or quantity, and their distribution is determined by the structures of the differentiating limb. He also showed that nerveless or poorly innervated limbs develop normally, indicating that morphogenesis is independent of innervation and function.

Fetal movements of mammals, both respiratory and general, have been intensively studied in recent years, especially by the Barcroft group at Cambridge, and Windle and others in America. Windle has produced evidence that the presence or absence of spontaneous fetal movements at certain periods of fetal life depends on the amount of calcium or potassium in the surrounding medium. He suggests that the reaction is in the peripheral motor mechanism rather than in the central nervous system, possibly involving the skeletal muscles alone or the peripheral motor

nerves or nerve endings. Straus has shown that muscular movements may be elicited in rat embryos by electrical stimulation through the skin, or direct nerve stimulation at sixteen days, but not at fifteen. Since there is so little difference in the structure of the muscle fibers of the fifteenth and sixteenth day, he concludes the difference in response is probably due to extramuscular factors.

Barcroft (1) reviews the work of his group on the development of the neuromuscular mechanism and Barcroft & Barron (2) add more recent data. Perhaps their most important paper is, however, an earlier one [Barcroft & Barron (1)] which presents most of the data on which their conception of the problem has been founded. In general, they believe that both the "total pattern" school of development of fetal behavior and the "reflex" school are partly right. We may best summarize their views by quoting directly from the abstract of their second paper:

> Observations on the prenatal development of the sheep indicate that the first responses to the stimulation of peripheral sensory nerves, whether they be exteroceptor or proprioceptor, and regardless of their area of distribution, are restricted in the amount of musculature they involve. As development proceeds, the responses aroused by some nerves, mainly those distributed to what we have regarded physiologically as the head, become more and more extensive. Other nerves—notably those to the trunk—never attain the ability to arouse such extensive reactions. Inasmuch as the nerves to the head appear to develop most rapidly, the extensive responses appear early in behavior. Just when the first local responses appear to be aroused from the trunk has not been definitely determined. However, of these two responses the extensive, when it occurs, appears dominant and the localized response secondary in the same sense that the head of an animal is its dominant part, the trunk the secondary.

Barron makes clear in his abstract their conception of the functional development of the brain, the basis of which is that the bulbar-spinal mechanism is progressively inhibited by the "functional development of neurones lying further and further forward in the brain stem; for surgical removal of the appropriate forward parts of the neuraxis causes the older types of movements to reappear again." Kuo, using chick and frog embryos, has come to practically the same conclusion.

Excretory system.—In spite of the anatomical and probable physiological importance of this system in development, relatively little physiological work has ever been done to correlate its function with its ontogeny. Most of our assumptions in regard to it are based on morphological and teratological observations. Keosian

has found the fluid taken from mesonephric tubular cysts growing in tissue culture to be four to fifteen per cent more dilute than the surrounding medium. The cyst fluid contains no protein, indicating that the fluid accumulates against the colloid osmotic pressure of the surrounding medium which does contain protein. Accumulation also proceeds against hydrostatic pressure and a progressively increasing concentration gradient. Cameron & Chambers found that in fragments of a three and one-half month human fetal metanephros grown in tissue culture with phenol red and orange G the fluid in closed portions of proximal tubules (cysts) is maintained at pH 7.0 or less in a surrounding medium of pH 7.4 to 7.6. Flexner (2) investigated chemical changes occurring in the developing metanephros when inactive nephrons change to secretory organs. To quote:

> Results indicate onset of tubular secretory activity is accompanied by these changes: 1. In pre-secretory stage cytochrome oxidase is in low concentration and equally distributed between epithelium and stroma. In secretory stage, oxidase increases markedly in epithelium and disappears from stroma. 2. In pre-secretory stage, redox potentials of epithelium and stroma are alike. With onset of secretion, the potential of epithelium rises and that of stroma falls so that a difference of 0.230 volt develops between them.

Alimentary system.—Ehrhardt injected thorium dioxide solution (thorotrast) into the amniotic sac through the body wall of a woman fifteen hours before the necessary termination of pregnancy by Caesarian section at five to six months. He shows a roentgenogram of the fetus with a heavy deposit of thorium in the lungs and a dense shadow of the esophagus, stomach and considerable portion of the small intestine. While this is a clear demonstration that the fetus both breathed and swallowed amniotic liquor, it is possible that this occurred only after the beginning of the anesthesia. Windle & Bishop found gastrointestinal motility in cat fetuses, previously decerebrated, delivered by Caesarian section without anesthesia and with intact placental circulation. As anoxia was increased the movements were typically exaggerated and manifested in turn propagation peristalsis, rhythmical segmentation, pendulous writhing and finally loss of tonus in extreme asphyxia. Windle, Becker, Barth & Schulz placed thorium dioxide in the amniotic cavities of guinea pig fetuses from midterm to term. Their results showed that amniotic liquor is swallowed as early as the fortieth day and that soon after material

traverses the intestines by peristalsis and concentrates in the large intestine. Meconium passes a few days before birth, mixes with the amniotic liquor, and is swallowed.

Cerebrospinal fluid.—Flexner (1) showed that in the fetal pig, chloride, sodium and urea in the cerebrospinal fluid are in equilibrium with the blood plasma up to the fortieth day but at forty-three days they are not. During this three-day interval he believes the fluid changes from an ultrafiltrate to a secretion. Cohen & Davies report that in the chick, rabbit, rat, guinea pig and mouse embryos the first escape of cerebrospinal fluid from the central nervous system is coincident with the development of choroid plexus membranes in the roof of the fourth ventricle. In all stages these two areas in the rabbit, rat and guinea pig are impermeable to a one per cent double solution of potassium ferrocyanide and iron ammonium citrate injected under normal conditions into the central nervous system. Under the influence of hypertonic saline in the blood stream, they become permeable and permit extracerebral passage of dye from the fourth ventricle, but only after the choroid plexuses are differentiated.

Special sense organs.—Rawdon-Smith *et al.* obtained the Weaver-Bray effect from fetal guinea pig ears at the fifty-second day.

Fetal membranes.—Important as is the physiology of the placenta, it is impossible to enter into this large field here. For a review of this material consult Needham (1) and Mayer, Vogt & Seitz.

Summary

From the physiological point of view the most important results of recent researches are the demonstration: (1) of artificial parthenogenesis in mammals; (2) that organizer areas possess a type of metabolism different from that of the rest of the embryo; (3) that insect metamorphosis is at least partly controlled by an endocrine system; (4) that sex hormones are an intermediary mechanism in the expressing of genic sex constitution in Amphibia, Reptilia, Aves and Mammalia; (5) that radioactive tracer compounds are useful in studying embryo physiology; (6) of the manner of initiation and development of the mammalian heart beat; (7) of the probability that the foramen ovale is controlled by rhythmic muscular contractions of its valve; (8) of the fact of normally occurring fetal respiratory and swallowing movements

in utero; and (9) of the manner of development of the whole neuromuscular activity pattern in mammals.

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RESPIRATION

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"Respiration" originally referred only to the inspiration and expiration of air. This meaning was later enlarged to include gaseous exchanges which take place principally by diffusion, as in leaves of plants or tracheae of insects, extraction of dissolved gases from water by aquatic forms, the gaseous metabolism of isolated organs and tissues, and in some cases the utilization by bacteria of substances other than oxygen and the production of substances other than carbon dioxide. Last year's article treated mostly respiration in the higher animals and particularly the nervous mechanisms involved. We shall try to cover less intensively a larger field, reviewing work that deals with three stages of gaseous exchange: utilization and production in the cell, transport within the organism, and transfer between organism and external environment.

Plants, Including Bacteria

The effects of a large number of substances upon the rate of respiration in yeast were followed by Wolf, and the energy balance sheet of the metabolism of yeast has been worked out by Winzler & Baumberger. Starved yeast (Fleischman G.M. 139) put in glucose solutions respires at a constant rate for two hours, then the respiratory rate declines, assimilation takes place, and the yeast grows (Stier & Newton). Williams tabulated the optimal oxygen tensions for thirty-five pathogenic fungi and showed that the optimal tension varied with the culture medium. The uptake of oxygen by tubercle bacilli, studied by Nakamura in both avian and human types, was greatest at pH 7.2. It was increased by glycerol or by small amounts of inorganic iron.

Nielsen & Dresden found that the temperature coefficient of the respiration of *Aspergillus niger* decreases with increasing temperature up to 37°C. and is independent of the age, growth, and activity of the mycelium, while the rate of respiration is inversely proportional to the percentage of dry weight, which is a function of its age.

The curious metabolism of the sulphur bacteria is exemplified by a motile vibrio which Edington found in a lead mine dehydrogenating a substrate with the formation of hydrogen sulphide.

The respiratory block in dormant spores of *Neurospora tetrasperma* is attributed by Goddard & Smith to inactivity of carboxylase. The effects of temperature and light on the gaseous exchanges of eleven species of lichens have been observed by Stålfelt. Gaffron (1) suggests that under certain limited conditions of dim light, shortly after the oxygen in the solution has been all used up, green algae may reduce carbon dioxide with molecular hydrogen. He also finds (2) that these algae have persistently high respiratory quotients (1.0 to 2.0, averaging 1.4) in sugar solutions. Such high values have previously been reported chiefly in succulent plants and fruits which store organic acids, but some other explanation must be sought for the unicellular *Chlorella* and *Scenedesmus*. Lundegårdh (1) found that the respiration of wheat roots was stimulated by manganese and thinks that this element may play a role analogous to that of iron in animals. He has also proposed an electrochemical theory of salt absorption and of respiration, based principally on measurements of membrane potentials (2).

Hill has prepared cell free suspensions of the chloroplasts of various angiosperms by emulsion in isotonic sucrose and has estimated oxygen production and absorption in these suspensions by spectrographic measurement of hemoglobin and myoglobin added to them. Oxygen is evolved in light when either leaf extracts or ferric salts are present. Photoreduction of ferric oxalate to ferrous oxalate and oxygen is especially vigorous. This reaction is unique in biochemistry. French has derived a satisfactory relation between the light absorbed and the assimilation of hydrogen and carbon dioxide by *Streptococcus varians*, showing that the over-all reaction takes four quanta.

Invertebrates

The sponges, lamellibranchs, and tunicates extract less than a fifth of the oxygen in the water they take in, while the annelids, crustaceans, gastropods, cephalopods, echinoderms, and fish extract about half (Hagelhoff). Many of the littoral coelenterates, molluscs, annelids, echinoderms, crustaceans, and fish, vary in

their oxygen consumption with the tides and time of day. The oxygen consumption is greatest at high tide and least at low tide, and this is true even in those animals which are exposed at low tide. This rhythm persists for some days after the animals are brought into an aquarium (Gompel). The respiratory movements and volume have been studied in *Phryganea* larvae, the marine worms *Arenicola* and *Nereis*, and the fresh water clam *Anodonta cygnia* (van Dam). The rate of respiration in the crayfish has been shown to vary directly with the carbon dioxide and inversely with the oxygen content of the water (Peters), and the amount of oxygen absorbed is increased, and in some cases doubled, by the injection of 2,4-dinitrophenol (Serfaty). Korr presents evidence for a change in the respiratory mechanism in the sea urchin egg with fertilization from a non-iron-containing carrier in the unfertilized egg to a cytochrome-indophenol-oxidase system in the fertilized. The experiments show differences in susceptibility to cyanide poisoning and differences in temperature characteristics. Davey has found the intestinal nematodes of sheep capable of enduring a short, but not a prolonged anaerobic existence. *Ascaris* and *Ancylostoma caninum* will use oxygen readily when it is available. Davey considers it possible that nematodes may require hemoglobin for an aerobic life (because the oxygen tension in the intestine is so low) and may be able to synthesize it. In blow fly larvae Fraenkel & Herford have shown a slight respiration through the skin when the spiracles were ligated. Fox has shown that the crown of *Spirographis* is a respiratory organ.

Cold-Blooded Vertebrates

Von Ledebur in his review adopts the view that oxygen secretion takes place through one respiratory plaque or rete mirabile in the swim bladder of the fish, and oxygen absorption through the other, and that this mechanism makes possible regulation of buoyancy.

Smyth finds that, in the frog, inspired carbon dioxide initially inhibits respiration by means of a reflex mediated by vagal afferents from the larynx; after one or two minutes stimulation occurs, probably of central origin. Oxygen lack arouses hyperpnea, depending partly on a carotid gland mechanism, thus suggesting an analogy to the carotid body of mammals. The respiratory center

in the medulla is similar in its functions to that of mammals, but since carbon dioxide can be excreted if necessary through the skin, and because of special vascular mechanisms, pulmonary ventilation is regulated almost exclusively by the degree of oxygen lack and not by carbon dioxide.

The laryngeal movements of the amphibia and many reptiles are related principally to smelling and not to breathing. The influence of carbon dioxide is in general to increase the breathing, but in *Alligator mississippiensis* and *Opisamus apus* carbon dioxide inhibits the respiratory movements (Vos).

Mammals

Neurology and anatomy.—By electrical stimulation in limited areas of the medulla of the cat, Pitts, Magoun & Ranson have localized the respiratory center in the ventral reticular formation of the medulla, dorsal to the cephalic four-fifths of the inferior olive. There are in this area two centers, one which stimulates, and one which inhibits, inspiration. These centers are bilateral, are closely related synaptically, and show neurological relations that can only mean reciprocal inhibition. They are apparently also influenced by the vagal nuclei in the tractus solitarius, since weak stimulation of the central end of the vagus facilitates inspiration, while strong stimulation facilitates expiration. The authors have tried, apparently successfully, to show that they have not been stimulating descending pathways to the respiratory muscles or collaterals leading to other centers. They have prepared animals in which the possibility of vagal or higher pneumotactic mechanisms has been ruled out surgically and have shown in these preparations that apnea to the point of death results from maintained stimulation of the inspiratory center. By appropriate stimulation of the inspiratory and expiratory centers, Pitts, Magoun & Ranson could produce any type of respiration they pleased, and they do so in every preparation. Their work makes Lumsden's conclusions doubtful and seems to weaken Gesell's position (1), for nobody has ever shown that changing the reaction of the *milieu intérieur* has different effects on different parts of the central nervous system or even on different peripheral nerves.

Stella (1, 2) has published a number of papers of anatomical interest. He holds that respiration is independent of the inferior

corpora quadrigemina and the red nucleus. In the upper part of the pons is a center that rhythmically inhibits inspiration and thereby produces normal respiration. Apneusis is independent of afferents from the fifth, seventh, and eighth cranial nerves. He claims that this center is stimulated by carbon dioxide, although he did not report the arterial pCO_2 in his experiments. The apneustic center is normally inhibited rhythmically by afferent impulses through the vagus nerve. The pneumotaxic center he believes, in opposition to the views of Henderson & Sweet, is bilaterally situated near the midline in the ventral part of the cephalic end of the tegmentum of the pons, and its connections with the apneustic center are said to be homolateral. Stella (3) has also revived the notion that the cerebellum controls respiration in some way. After removal of the cerebellum, the arterial pressure remained fairly constant in his preparations, and the respiration increased either in rate or in depth. A conclusion that the cerebellum normally exercises tonic restraining influences on the respiration is perhaps hardly justified.

Fleisch & Tripod could find no afferent nervous pathways essential for regulating the fundamental rhythm of the respiratory center. Wyss has examined electrically the volleys of impulses that come from the central end of the cut phrenic nerve in dogs. When dyspnea was present, synchronized impulses came down the nerve. There was no synchronism when the animal was breathing quietly with its chest closed. Rijlant (1, 2) has proposed a complex mechanism of respiratory control by two centers, one high in the medulla that sends out a steady stream of impulses which are modulated into the proper rhythm for breathing by a center slightly lower down.

Smith has made what seem to be important observations on the cerebral representation of respiratory movements. He finds in cats, dogs, and monkeys (*Macaca mulatta*) that electrical stimulation of the cortex in area 6*a* (of Brodman) accelerates respiratory rate and increases depth and that stimulation of area 6*b* has an inhibitory effect. Stimulation of area 6*b* also inhibits respiratory changes normally caused by afferent impulses.

Mention only can be made of Boriani's attempt to localize cerebral centers, Gesell's paper (2) on the integration of the respiratory act, and Nogami's study of mitochondria, metachondria,

and Golgi apparatus in the lung parenchyma. The crossed phrenic phenomenon is discussed by Rosenblueth, Klopp & Simeone. Rudberg has confirmed the older observations that clamping off the common carotid of cats and rabbits increases the respiratory rate and depth. He adds the observation that this respiratory stimulation is greater when the arterial blood pressure is below a certain critical level. Hammouda & Wilson defend the thesis that duration of expiration is not a function of the depth of inspiration or its duration and claim that there are two functional types of vagal endings in the lung, one mediating impulses inhibitory to respiration, the other excitatory.

The most recent and best review of the peripheral regulators of respiration is by Heymans & Bouckaert. Comroe finds that the aortic body is a chemoreceptor essentially the same functionally as the carotid body. In cats its blood supply comes from the coronaries; in dogs, from the vasa vasorum of the aorta. In dogs the aortic body is predominant over the carotid body in producing hyperpnea and vasomotor changes, but in cats the carotid body is quantitatively more important than the aortic. Bernthal & Weeks have examined the effect of perfusing the carotid body with fluid at different temperatures between 15°C. and 45°C. They found that as the temperature of the carotid body increases, there is vasoconstriction and increased rate and volume of respiration. Partridge has found that the acceleration of respiratory rate caused by electrical stimulation of vagi cooled to 8°C. is effected by stimulation of cardiac afferent fibers. If the lungs are distended, the acceleration is the result of activity of the depressor mechanism of the carotid sinus.

Dijkstra & Dirken have shown that forced breathing in rabbits increases the motor chronaxie of the sciatic nerve measured percutaneously, but has no effect if the nerve is exposed or if the sympathetic innervation of the area is destroyed. Hyperventilation, therefore, changes the skin impedance, not the properties of the nerve.

Bayliss & Robertson have measured separately the viscous and elastic properties of lungs and have proposed as quantitative measurements of these properties the indices "viscance" and "elastance," which in some cases seem to vary independently of each other.

Fetal respiration.—Barcroft & Barron have reviewed recent work, much of it in Barcroft's laboratory, on fetal movements, including those depending on oxygen lack. Barcroft, Kennedy & Mason have made a direct determination of the oxygen consumption of fetal sheep and from their data calculate the rate of umbilical blood flow and the lower limit of blood flow in the uterus. Fetal respiration is purely a matter of transport of metabolites by the maternal and fetal circulation. Rosenfeld & Snyder have shown in rabbits that the stimulation of respiratory movements by carbon dioxide, anoxia, or hydrogen cyanide first appears when the fetus is viable. Before this time, respiratory movements appear, but they are unaffected by carbon dioxide, anoxia, or hydrogen cyanide. The normal transition to adult respiratory patterns appears at birth, rather abruptly.

Windle & Barcroft observed rhythmic respiration in the chick on the eighteenth day of incubation and could initiate it four to six days earlier by 1.6 per cent carbon dioxide or less certainly by low oxygen. The increased respiratory rate shortly before hatching depends on a drying of the allantois and reduced permeability to carbon dioxide and oxygen (Windle, Scharpenberg & Steele). It has been found by Windle & Nelson (1) that in unhatched ducks carbon dioxide increases the respiratory rate when it acts by vascular channels, but slows the rate when taken into the lungs. Low oxygen content of the inspired air increases the respiratory rate. Pulmonary respiration starts three days before hatching. They also found (2) that severing the vagus of young ducks high in the neck produces a dyspnea subject to relief by breathing five per cent carbon dioxide. Evidently in the duck inhibitory receptors in the lower respiratory passages are activated by carbon dioxide.

Barcroft, Barron, Cowie, *et al.*, have studied the effect of asphyxia in eliciting respiratory movements in the fetuses of goats. At one hundred days, an oxygen saturation of 25 per cent in the umbilical vein produces gasping in the fetus, but at term the saturation has to drop to 15 per cent before respiratory movements start. Steele & Windle have found the same effect in cats. Barcroft, Barron, Kramer & Millikan have observed in sheep fetuses that the carotid arterial saturation rises from 40 per cent to 90 per cent shortly after birth and that there is a concomitant rise of about 40 mm. Hg in the carotid arterial blood pressure.

Roos & Romijn have studied the blood gases in oxen. The oxygen capacity of fetal blood is greater than that of the corresponding maternal blood. Both have increased oxygen capacities after parturition. The oxygen dissociation curve of fetal blood is to the left of that of the maternal blood. There is fifty per cent saturation at 11.5 mm. Hg in fetal blood and at 34.5 mm. Hg in maternal blood, because the fetal hemoglobin differs from the maternal.

The sucking reflex is notably strong in young mammals. In newborn children the respiratory center has a slower fundamental rate than that for sucking. When food is taken, the sucking center imposes its rate upon the respiratory center (Peiper).

The congenital anomalies of the human heart and circulation deserve closer study from a physiological rather than a diagnostic standpoint. Some cyanotic patients go for years with very low arterial saturations. Surely their means of combating anoxemia are interesting. A step in this direction has been made by Hallock, who estimated the blood lactate of some thirty patients with congenital anomalies and found it normal at rest but high in those of the cyanotic group after mild exercise.

Pharmacology.—Courtice, Douglas & Priestley (1, 2) confirmed their earlier observations that during a walk of ten miles the respiratory quotient rose toward a carbohydrate level and stayed there until the end of the walk. During recovery it dropped to a predominantly fat level, and the subject usually developed a ketonuria and ketonemia. Epinephrine injected subcutaneously either during rest or during mild exercise raised the respiratory quotient. They accounted for the whole change by the lactic acid that accumulated in the blood.

Bartsch reports that veratol increases the vital capacity by some twenty per cent, by increasing the efficiency of the left ventricle, thus leaving less blood in the lungs. Sheldon has found in parturient women that, with most barbiturate analgesias, the vital capacity is decreased considerably and remains low for a considerable time. Pregnancy *per se* does not change total lung volume, and without drugs there is only a slight and transient *post partum* decrease.

Butturini & Capuzzi have studied the effects of amphetamine (benzedrine) on human respiration. Berggren & Söderberg showed that oral doses of 20 mg. of the drug increase the basal metabolic

rate and also increase temporarily the cardiac output. Michelsen & Verlot observed in dogs, moribund from respiratory failure induced by pentobarbital anesthesia, improvement in the respiratory rate and volume and in the arterial oxygen saturation when treated with amphetamine. A favorable effect was also observed on administering the drug to rabbits in avertin anesthesia.

West has completed a study of the effects of curarine upon the respiratory tract. He maintains that it causes a direct bronchial and bronchiolar constriction, with a curare-like effect upon the respiratory muscles, with consequent reduction in the capacity of these muscles to maintain contraction, and a great flaccidity, especially of the diaphragm. This causes weak inspiratory efforts, a reduction in thoracic volume, and an increase in pressure in the potential pleural cavity. Sudden respiratory failure in these animals is caused by acute pulmonary collapse.

Petrovskaia has tested the effects of atropine, acetylcholine, epinephrine, and ergotoxin on the perfused lungs of guinea pigs. Epinephrine has a pressor effect on pulmonary arterial pressure (reversed by ergotoxine) and dilates the bronchi. Acetylcholine constricts the bronchi and in small doses has a depressor effect on pulmonary arterial pressure.

Henderson & Rice have reinvestigated the effect of morphine on respiration in rabbits. They find that the cells of the central nervous system that control respiration become less sensitive to carbon dioxide. Ether, on the other hand, increases this sensitivity and is to some extent an antagonist to morphine. Coramine has a sensitizing effect, but is less consistent than ether, although it increases the tonus of the respiratory muscles of the animal.

Jeney & Vályi-Nagy have shown that the oxygen uptake of cats can be raised by 50 per cent by 2, 4-dinitrophenol, that quercitin depresses the oxygen uptake and can partially inhibit the rise due to the other drug. Other pharmacological studies have been made by Nowak on pernocton, sodium amytal, and avertin and their effect on the carotid sinus; by Schweitzer & Wright on prostigmine and acetylcholine; by Hazard & Jequier on theophylline; by Santenoise, Frank, Grandpierre & Vidacovitch on vagotonin; by Nicholson & Sobin on the application of nicotine and lobeline to the floor of the fourth ventricle; and by Marri on the disturbances caused by intravenous injections of procaine hydrochloride in association with epinephrine.

Curtillet & Curtillet have made a microscopic study of air embolism in frogs and in rabbits. The emboli that lodge in the arterioles are absorbed in a few minutes. Eckhardt has shown that barium sulfate embolism in the lungs of dogs leads to a transient decrease in the coronary circulation, and after half an hour to an increase. This is not a cardiopulmonary reflex since it occurs in animals whose lungs have been denervated.

Respiration in tissues and organs.—We should like to point out again the relation between specific dynamic action and the oxygen uptakes observed by the tissue respiration workers. In general, those substrates that cause a vigorous oxygen uptake with liver or muscle slices in the presence of oxygen have a specific dynamic action, provided they are not toxic to the test tissue. Lusk fathered the idea that Liebig lost his point in maintaining that metabolism is conditioned by the supply of foodstuffs, not by the needs of the organism. The "mysterious drug-like action of proteins in stimulating metabolism" we conceive to be analogous to, if not identical with, the extra oxygen uptake caused by added substrates. Field, Belding & Martin have determined both the basal metabolic rate of rats and the oxygen uptake of slices of their tissues. The sum of the tissue oxygen uptakes was about 66 per cent of the basal metabolism. We think it fair, within limits, to argue from isolated systems to the whole animal. Rotta & Stannard have shown that muscle alone of frog tissues can repay an oxygen debt after a period of anoxia. Nerve, cardiac muscle, intestines, stomach, kidney, and liver cannot. Skin does to a small extent. It will be interesting to see if mammalian tissues as well show this phenomenon, because the distribution of the oxygen debt has remained unknown.

The respiration of individual organs, tissues, and cells is usually studied solely in relation to the metabolism of particular substrates, not from the standpoint of general respiration. Wooldridge & Higginbottom have started interesting work on the effects of toxins on tissue metabolism. They find that the alpha toxin of *Clostridium perfringens* (*welchii*) inhibits the succinic dehydrogenase system of the minced small intestine of guinea pigs. This effect is reversed by antitoxin and is not an inactivation, but a reversible inhibition of the succinic dehydrogenase.

Asmussen, Christensen & Nielsen have made an estimate of

the metabolism of the leg by taking the difference in metabolism between the whole body at rest or at work, and of the body with one leg isolated from the systemic circulation by a sphygmomanometer cuff. In rest they estimate the oxygen consumption of the muscle to be about 2 cc. per kg. per min. and at work about 110 cc. per kg. per min. They estimate the maximum oxygen uptake of the leg muscles to be about 180 cc. per kg. per min. Stannard finds that the oxygen consumption of resting frog muscle is not sensitive to azide, but the oxygen consumption of working frog muscle is sensitive. In a series of papers on the respiration of dog gastrocnemii, Quensel & Kramer, and Kramer and associates (1, 2) have used the photoelectric method of measuring the oxygen saturation in flowing blood. In a prolonged tetanus, oxygen consumption sets in simultaneously with the stimulus, and an oxygen debt is contracted. In muscles stimulated 34 times a minute, a steady state of oxygen consumption may be reached, and oxygen consumption may parallel work done so long as further vasodilatation is possible. Lactic acid comes out of muscle even at rest. This output increases immediately when contraction occurs, and is not proportional to the work done but is roughly proportional to the degree of anoxemia.

A good deal of research is being done on the isolated heart in the heart-lung or heart-oxygenator circuit. For example, Bogue, Evans & Gregory have demonstrated with dogs that the heart glycogen is depleted by epinephrine, much less by anoxia induced with nitrogen or cyanide, but that a combination of epinephrine and anoxia has an effect larger than the sum of the two separate effects. Gauer & Kramer have reinvestigated the effect of epinephrine on oxygen consumption of isolated cat hearts. They use the indirect method of calculation from the arteriovenous difference and the total coronary flow. After epinephrine administration there is coronary dilatation without extra oxygen consumption. In other conditions also there is no specific stimulation of oxygen consumption per beat with work constant, unless the heart has stopped and is stimulated to beat again by the drug. Gollwitzer-Meier & Kroetz have also studied the isolated heart.

Levy, Light & Blalock have shown that in dogs with experimentally induced renal hypertension, oxygen consumption of the kidney whose renal artery has been clamped is decreased below its

normal value. Using Kramer's photoelectric method of continuous records of blood oxygen saturation, Kramer & Winton measured arteriovenous difference, arterial pressure, blood flow, and urine flow of kidneys in a lung-pump-kidney circuit. With a rise of blood pressure, there are first transient effects in the form of lessened arteriovenous difference, increased blood flow which overshoots the needs of the organ, and increased diuresis. Second, there are permanent effects in the form of a return of the arteriovenous difference to its original value, increased oxygen consumption, and marked diuresis. Accompanying increased urea concentrations in the blood, there is first a transient antidiuresis with first decreased, then increased oxygen consumption and a permanent effect consisting of diuresis and an unchanged oxygen consumption. Therefore, urine formation and oxygen consumption are not simply related. Becker, Hanstein & Schäfer have compared the oxygen uptake of kidneys of guinea pigs both *in situ* and *in vitro*. The average oxygen uptake of kidneys in situ was 90 c.mm. per gm. per min. The average uptake of slices in the Warburg apparatus was about 45 c.mm. per gm. per min. There was no variation with the age of the animal.

Deutsch & Raper have been able to estimate the respiration of submaxillary gland tissue at rest and when stimulated by acetylcholine and have demonstrated by the use of fluoride and iodoacetate that it is quantitatively and qualitatively different in the two conditions.

Brinkman & Wildschut have investigated the rate of reduction of hemoglobin in human fingers that are cut off from the systemic circulation. They find that there is an optimum pO_2 for reduction and that if the pO_2 is either much above or much below this optimum the rate of reduction is slow. This finding agrees with those on the mechanism of oxygen poisoning. Lee & Chen have found that the rate of proteolysis by acid glycerol extracts of sheep livers is diminished by high partial pressures of oxygen. This inhibition is only partly reversible.

Diving mammals.—The problems relating to diving animals have been reviewed by Irving. The possible oxygen stores are inadequate to explain the ability of the seal, for example, to stay down from five to ten times as long as a man of the same size. Irving gives the following table of oxygen stores, to which we have added Robinson's figures for the seal:

	Man	Hypothetical Diving Animal	Seal (Robinson)
	ml.	*ml.*	*ml.*
Lungs	900	1,500	545
Blood	1,160	1,600	2,055
Fluids	245	245	245
Tissue respiratory pigments	335	670	2,530
Fats		250	
Total	2,640	4,265	5,375

He then discusses lowered metabolism as a possible explanation, discards that, and finally chooses circulatory changes, which he believes largely close off the blood supply to all parts of the animal but the heart, lungs, and brain. In support of this he cites the slowing of the heart reported in seals and beavers when they dive, and in certain conditions in ducks. He also cites the existence of a muscle band around the vena cava in many diving forms and the large plexus of veins in the abdomen. Muscles, if not used too vigorously, could easily support fifteen minutes of anoxemia. Diving animals are relatively insensitive to carbon dioxide and often breathe irregularly out of the water. Robinson measured the amount of muscle hemoglobin in the seal (which Irving had assumed to be less than one per cent, as in the dog) and found it to be about eight per cent. This great amount of muscle hemoglobin would permit the storage in the muscles of a 70 kg. seal of about two liters more oxygen than Irving calculated. Irving's argument with Robinson's supplement is very convincing.

Muscle hemoglobin has been reviewed by Millikan. He considers its function in most animals is to act as an oxygen store over short periods of the order of a second.

Scholander estimates that the collapse of the whale's lung is so complete during a deep dive that all the residual air is in the thick-walled bronchi and bronchioles, which, as the pressure increases, resist collapse longer than the soft alveoli. The walls of these bronchi are so thick that nitrogen does not diffuse through them in dangerous amounts, hence the animal's freedom from the bends. The failure to get oxygen from the lung he considers of little importance, as the circulation is probably much restricted, and

in any case the animals exhale deeply before submerging. He has demonstrated that a frog compressed in water and not allowed to breathe will not suffer from the bends on decompression, which develop if the animal be allowed to breathe while compressed.

Anoxia.—Bouckaert, Heymans & Samaan report that in the dog, whether anesthetized or not, hypoxemia stimulates respiratory and vasomotor centers primarily by means of the carotid sinus and vagus nerves, the chemoreceptors of which are located in the carotid body and in the cardioaortic vascular area, the vagal chemo eceptors being less important. Carotid sinus and vago-sympathetic-aortic nerves are essential to stimulation by oxygen lack; in their absence low oxygen depresses respiration (Bouckaert, Grimson & Heymans). Jongbloed deprived dogs of aortic and vagus nerves and found that, as weeks passed, the response to low oxygen returned towards normal as a result, he thinks, of regeneration. When the chemoreceptors of the aorta and carotid sinus are depressed, accumulated unoxidized end-products first stimulate, but then depress, respiration. The influences of carbon dioxide and of low oxygen on the carotid sinus are attributed to the same chemoreceptors by von Euler, Liljestrand & Zotterman. Comroe & Schmidt produced greater reflex hyperpnea in dogs by stimulating the carotid body with low oxygen than with carbon dioxide. They consider the carotid body specialized for response to interference with oxidations within itself. Its resistance to depression qualifies it to sustain life when the respiratory center has gone out of action. It may constitute an accessory mechanism brought into action only in emergencies.

The recovery of the sympathectomized dog and his ability to carry on exercise does not indicate an essential role of the carotid sinus in so far as it depends on the sympathetic system. McDonough found normal and sympathectomized dogs stood six per cent oxygen for some hours equally well; they tolerated four per cent oxygen for 145 and 102 minutes respectively.

The effects of insulin treatment in schizophrenia have been attributed to reduced oxidation in the brain. Gellhorn, Ingraham & Moldavsky conclude that the reduction in rate of oxidation in the brain thus produced is greater than in other tissues and is greater than is produced in the brain by breathing low oxygen. Much of our knowledge of brain metabolism rests on studies of isolated tissues. Laser finds that the aerobic glycolysis of retina,

liver, and other tissues is greater, and the respiratory quotient lower, in low oxygen than in pure oxygen, as a consequence of modified enzymic activity. Measurements of cell metabolism carried out in pure oxygen do not necessarily apply to the intact organism. In this connection Kempner reports that the respiration and the respiratory quotient of isolated cells in a physiological environment decrease with lowered oxygen tension. Other significant factors are pH, pCO_2, salt content, and temperature.

Alexander & Himwich treated schizophrenic patients by administering nitrogen, reducing arterial oxygen to two vol. per cent in three to four minutes. Respiration increased until extensor muscle spasms occurred; it then became arrhythmic.

Two samples of alveolar air collected at 22,800 feet on the 1938 Everest expedition and sealed in glass bulbs had a carbon dioxide tension of 16.5 mm. and an oxygen tension of 35.7 mm. (Warren).

Campbell (1, 2) has made numerous studies of the effects of diet upon the susceptibility of white rats to acute anoxia. He holds that they die because of intoxication from breakdown products of histamine and histidine which are normally oxidized. Vegetable fiber, carrots, low protein, and glutamine are all protective.

Dick finds that intravenous oxygen in dogs paradoxically causes acute anoxemia by giving temporary pulmonary embolism. There is marked increase in ventilation, just as one observes clinically in cases of air embolism, and this increase lasts long after the oxygen has been absorbed.

Moschini has discussed human respiration under the influence of various gaseous pressures, and Shoji, the various mechanisms of adaptation to low oxygen and high carbon dioxide. Kruglyi has observed that gastric motility of dogs is abolished by very low oxygen pressures. Goebel & Marczewski have exposed dogs for ten hours every day for two months to an atmosphere approximating 10,000 meters and find that the blood pH decreases to 7.05, the alkali reserve to 32.8 vol. per cent, the oxygen capacity of the blood increases, and the red cells increase. This process is increased in speed by prolonged treatment with ammonium chloride. Wilbrandt, Wilbrandt & Steinmann used the interferometer to study the adaptations to quick changes in barometric pressure. They showed that at 3,450 meters resting ventilation is twenty to thirty per cent higher than at 2,060 meters and is higher than one would calculate from the increased muscular effort in

breathing. With each step up, the respiratory quotient increases; with each stage on the way down it decreases. These changes can be explained in terms of retention and loss of carbon dioxide, and oxygen debt.

Van Harreveld & Marmont have made observations on the important subject of the functional recovery of the spinal cord from periods of complete anoxia. They asphyxiated cords of spinal cats by raising the dural pressure above the arterial. After long asphyxia (fifty-five minutes) the tendon reflexes returned for forty-eight hours and then disappeared. Moderate extensor tone of reflex origin might return, but the tendon reflexes were lost for good. Histologically, it could be shown that the anterior horn cells were the most severely damaged structures of the cord.

High oxygen pressure.—Oxygen poisoning is still an obscure condition. Bennett & Smith have shown that in the rat prolonged exposure to four atmospheres of air leads to sclerosis of the arterioles of the lung and subsequent hypertension in the pulmonary artery with dilatation of the right ventricle. After decompression there is systemic arterial hypotension. Bean & Bohr have found that five atmospheres of oxygen first increase and then decrease the height of contraction by frogs' gastrocnemii and suggest, as a mechanism for oxygen poisoning, the irreversible inhibition of oxidative enzyme systems.

The problem of what starts bubble formation and subsequent air embolism in bends has not been solved. Haldane's pathological study on goats is not valid for slow ascents, and studies on diving mammals have not answered the question even for these cases. Behnke & Yarbrough have studied the narcotic effects of the inert gases argon, nitrogen, and helium at four to ten atmospheres. The narcotic effect and also the resistance to respiration increased with the density of the admixed gas, although at one atmosphere pressure no difference could be detected.

Bean & Rottschaffer have made a careful study of the poisoning effects of oxygen at five to six atmospheres' pressure upon decorticate dogs. The reactions of intoxication must arise from centers caudal to the anterior corpora quadrigemina, since neither cerebral cortex nor basal ganglia are necessary for their appearance, nor are the pressoreceptor or chemoreceptor mechanisms of the carotid sinus. The bradycardia is mediated by cardiovagal fibers, and vagal cold block is enhanced, thus indicating a paralysis

of normal vagal influence. However, the earliest signs of oxygen poisoning are alterations in the respiratory pattern. They suggest that oxygen poisoning is really carbon dioxide intoxication, although they made no analysis of blood. On the other hand, Behnke, Shaw and associates showed years ago that under similar conditions blood leaves the lungs with no higher carbon dioxide tension than usual.

Dogs, rats, rabbits, guinea pigs, mice, ferrets, pigeons, and sparrows are all killed by prolonged exposure to an oxygen tension of 760 mm. Soulié found more variation in susceptibility between individuals than between species. Most animals died on the third or fourth day, some lasted until the tenth, and one rabbit until the twentieth day. Animals could be made more resistant by previous prolonged exposures to oxygen or to irritant gases.

Exercise.—Christensen & Hansen (1) have compared the results obtained by using different methods of gas collection and find that subjects learn how to use the Krogh-Hansen mask more easily than they do the Douglas bag technique, but that trained subjects give the same results with either method. Asmussen, Christensen & Sjöstrand have found a close relation between vital capacity and blood distribution. The more blood there is in the periphery, the greater the vital capacity. Hitchcock & Ferguson have studied the changes accompanying standing up. Alveolar carbon dioxide tension decreases, there is retention of carbon dioxide and incurring of an oxygen debt, venous blood pressure of the arms decreases as that of the legs increases, and functional residual air increases. Christensen & Hansen (3) find that the respiratory quotient becomes greater than the resting value when the oxygen uptake of any muscle group rises to a certain threshold value.

The effects of prolonged work on respiration and metabolism have interested numerous workers. Christensen & Hansen (2) find that, even after long-continued work, carbohydrate makes up a considerable proportion of the metabolism. Libermann, Neknassow, Savtchenko, Slonim & Farfel find that the oxygen consumption of a trained subject remains constant throughout long-continued work, but in untrained subjects it goes up as they become exhausted. They attribute this in part to inefficiency of movement as co-ordination gets worse because of fatigue.

Szwejkowska has made a close analysis of the initial period of exercise. In moderate work, oxygen consumption and carbon di-

oxide output approach a steady state at the same time, but in severe exercise, oxygen consumption reaches a steady state before carbon dioxide output. This is probably explained by the output of lactic acid into the blood stream. Training decreases the length of time necessary to attain a steady state in exercise of a given intensity. Zaeper & Böhme have studied respiration and circulation during light and heavy muscular exertion by man.

Applied and clinical studies of respiration.—Ludwig has studied the effect of stenosis of the respiratory tract on efficiency. In particular, he finds that minute volume increases and vital capacity decreases when a subject puts on a German gas mask and that oxygen consumption and work efficiency decrease. These bad effects can be overcome to some extent by appropriate exercises. Enghoff has described a convenient and efficient portable half-mask. Boothby, Mayo & Lovelace have demonstrated the comfort and economy of the mask developed at the Mayo Clinic. Experiments with it indicate that pure oxygen at one atmosphere can be breathed for forty-eight hours without harm. Johnston, Sheldon & Newburgh have developed a respiration chamber for use with human subjects. The use of the Zeiss gas interferometer for physiological work was described by Wollschitt, Bothe, Ruska & Shenck. Wilbrandt has proposed certain simplifications that should make the method more widely applicable.

The increasing use of respirators is not being accompanied by careful studies of the effects of forced respiration. We should suppose the question of alkalosis and acidosis in these patients might be important. Kerridge has reviewed the advantages and disadvantages of various types of clinical respirators. Studies have been made by Mijnlieff & Waterman on the adaptations to anoxia and excess carbon dioxide made by organisms and the physiology of artificial circulation and artificial respiration. Seevers, Enzer & Becker have studied the adaptations made in silicosis and cardiovascular disease.

The clinical problem of dyspnea is as important as ever, but little new work has been done. Enghoff & Liedholm have reviewed Cheyne-Stokes respiration, and Comeau has written on the relation between it and atrioventricular conduction. Chapman, Dill & Graybiel have made a study of cardiovascular and respiratory efficiency in kyphoscoliosis. The vital capacity was reduced to about one-half, while the proportion of residual air was doubled.

There was no serious impairment of carbon dioxide or of oxygen transport, although dyspnea was habitual.

Brooks has found that appropriate breathing exercises conscientiously carried out markedly increase reserve air and residual air. The net effect is a considerable increase of total pulmonary capacity. Some asthmatics may be benefited by breathing under positive pressure. Barach & Swenson have studied the anatomical changes of the bronchi and bronchioles of such patients with the iodized poppy seed oil technique for outlining the lung spaces. They find that an inspiratory excess pressure of up to five cm. water and an expiratory excess pressure of up to eight cm. water maintain a larger lumen of the bronchi and of the bronchioles, and relieve dyspnea by overcoming the distressing resistance to expiration.

Dogs anesthetized with morphine and pernocton have normal sensitivity to oxygen lack but reduced sensitivity to carbon dioxide (Benzinger, Opitz & Schoedel). The importance of this fact in the use of mixtures of carbon dioxide and oxygen in the operating room is emphasized.

Thompson, Corwin & Aste-Salazar use spirograms in diagnosing mental disturbances. The pattern of respiration is the diagnostic criterion. In general, schizophrenics have a smooth spirogram, with respiratory excursions of about equal depth all the time. On the other hand, manic depressives tend to show a more uneven and irregular spirogram. These differences fit very well into the general pattern of behavior of the two types of patient and are susceptible of quantitative measurement.

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THE DIGESTIVE SYSTEM[1]

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General.—According to the observations of Crandall *et al.* (1) the P-P factor (nicotinic acid, nicotinamide or a substance capable of replacing it) is essential for the maintenance of normal gastrointestinal motility. Patterson, Smith & Hale (2) found that rats with blood 70 to 80 per cent saturated with carbon monoxide decreased their intake of food by 23 per cent; gastrointestinal peristalsis was inhibited by 33 per cent and egestion time prolonged by 22 per cent.

Animals with vitamin-B deficiency displayed a craving for fat and an aversion to carbohydrate and protein food (3). The aversion to carbohydrate and protein may result from a disturbance to gastrointestinal physiology produced in vitamin deficient animals, or it may be due to a disturbance in the metabolism of carbohydrates and proteins.

Myers & Davidson (4) observed in the human a retardation of propulsion through the gastrointestinal tract following the administration of Dilaudid, Eukodol, or morphine. Dicordid exerted less retarding action. The effect was apparently due to an increased tone of the sphincters and a decrease in intestinal propulsive motility. The administration of acetylcholine or pitressin was shown by Necheles & Masur (5) to exert a toxic action on the gastrointestinal tract. The action of acetylcholine was most marked on the upper portion; pitressin was especially harmful to the colon. Recent work on the relations of the endocrines to the digestive tract has been reviewed by Collip (6).

Salivary secretion.—Although the potassium content of muscle decreases with stimulation, the potassium content of the saliva and of the submaxillary gland, according to Wills & Fenn (7), remains relatively constant during electrical stimulation. Since glands stimulated by pilocarpine lost this restorative power as the output increased, pilocarpine appears to have some specific effect on the uptake of potassium by the gland. A difference between the

[1] This review covers, essentially, the period from July 1, 1938 to July 1, 1939.

effect of nerve stimulation and pilocarpine action was also noted by Brassfield & Hong (8): depression of the oxygen tension or elevation of the carbon dioxide tension of the blood during stimulation of the chorda tympani produced corresponding pH changes in the saliva and blood but no change in the rate of secretion; injection of lactic or hydrochloric acid produced no change in pH or rate of flow of saliva; but when pilocarpine constituted the stimulus, the pH changes were dissimilar and the rate of secretion did change. It was further noted that injection of sodium bicarbonate or sodium carbonate decreased the flow and increased the pH with both types of stimulation. Kesztyüs & Martin (9) reported that either sympathetic or parasympathetic stimulation of the submaxillary gland diminished the potassium, sodium, chloride and organic content of the saliva, in each case proportionately to the amount of secretion. Sympathetic stimulation gave saliva higher in potassium, calcium and organic content than chorda stimulation but lower in sodium and chloride. Apparently the calcium of saliva, following chorda stimulation, passed by simple filtration for its concentration lay between that of arterial and venous blood (10). At high altitudes there was a pronounced decrease in the salivary secretion of man, according to Krestovnikov & Maznichenko (11).

A protein formed by the salivary glands is reported to behave as a thromboplastin and to be responsible for the blood-coagulating action of saliva (12). Human saliva injected intramuscularly or intravenously into rabbits by Liaci (13) elevated the blood sugar; the effect was moderate if fasting saliva were used, more pronounced with saliva obtained after a mixed meal and most marked with saliva secreted after a pure carbohydrate meal. *In situ*, Bing (14) noted a rate of oxygen consumption for the submaxillary gland of 0.014 cc. per gm. per min. but apparently because of trauma, the rate in the Lindberg pump was only 0.003 cc. per gm. per min. and the venous outflow decreased four-fifths. Glands perfused with blood diluted with Ringer's solution increased in weight but those perfused with whole blood did not.

Chronic denervation of the submaxillary gland by excision of the superior cervical ganglion sensitized the gland (15) to pilocarpine, epinephrine and, less consistently, to acetylcholine. This suggests that the drug action was directly on the cells. However, Michelson (16) and Filippovich (17) present evidence which

indicates that epinephrine acts on the neuroglandular apparatus. Simeone & Maes (15) noted an increase in the responsiveness of the normal gland after cocaine administration but not in the gland sensitized by chronic denervation. Cocaine probably acts by acutely denervating the gland. Finch has shown that daily injection of pilocarpine (18) or atropine (19) results in small progressive increases in the rate of pre-injection secretion from the parotid gland. Starvation increased the volume of salivary secretion following both conditioned and unconditioned stimuli (20). The increase reached a maximum in the dog after 72 hours but after 96 hours returned to the 24-hour level. In atropinized animals application of hydrochloric acid to the oral mucosa led to development of a conditioned reflex (19) even though the unconditioned response was absent. The conditioned reflex underwent experimental extinction and exhibited spontaneous recovery.

The submaxillary saliva of the cat had a slight phosphatase action as compared with that of oral saliva (21). Human saliva had maximal phosphatase action towards glycerophosphate at pH 5.0 to 6.0. This activity was not entirely derived from epithelial scales, for common mouth organisms also exhibited marked phosphatase activity. Phosphatase activity, related to certain microorganisms, may be involved in calculus formation, e.g., *Penicillium* can precipitate calcium phosphate from calcium glycerophosphate. The secretion of the oral mucosa of man was found by Winson & Koschin (22) to be more viscid than saliva. Its secretory rate was increased by chewing dry bread.

In a human, devoid of salivary glands, Steggaerda (23) found that frequent drinking was necessary to relieve a dryness in the mouth not identical with thirst but the total daily intake of fluid was within the normal range. Administration of 100 cc. of ten per cent saline to this subject or to normal subjects produced definite thirst and augmented fluid intake. The augmented intake apparently was not necessarily related to the presence of a dry mouth. The intravenous injection of 300 cc. of five per cent saline reduced salivary flow to one-tenth the normal. The thirst which resulted could be prevented and the salivary flow kept normal by Holmes & Gregersen (24) if ingestion of 500 to 800 cc. of water preceded the saline injection. Kirk (25) found the tongue to be moist in 84 per cent of humans with normal intestinal activity, dry in 86 per cent of cases with motor paralysis, and normal in cases of mechan-

ical obstruction. Apparently the tongue condition was not related to plasma chloride concentration or to the degree of dehydration.

Fabian (26) has considered the relation of salivary and gastric secretion in health and disease.

Chorda stimulation, according to Arshovsky & Kriutchkova (27), produces saliva in the newborn. During development, this saliva remains constant in composition until the thirtieth to fortieth day when, coincident with the appearance of sympathetic innervation, its composition suddenly changes.

Plagge (28) found the difficulties in deglutition and the subsequent death from inanition which occurred in newborn rats deprived of two submaxillary and two sublingual glands or by duct ligation could be avoided if one gland were allowed to discharge normally or if the animal were forcibly fed.

Swallowing of contrast medium was noted in guinea pigs in amnion by Becker *et al.* (29) as early as the forty-second day. Shortly afterwards the thorium dioxide had left the stomach, intestinal peristalsis was noted, and near term the thorium was defecated.

Irritation of the respiratory passages or esophagus, such as occurs in gastroscopy, intratracheal anesthesia, etc., was found by Reid & Brace (30) to produce reflex stimulation of the vagi with modifications of the heart beat.

Richter & Maclean (31) found it desirable to distinguish between the concentration of salt solution at which subjects first recognized the difference in taste between salt solution and distilled water and the concentration at which they first definitely recongized the taste of salt. The former concentration is much lower than formerly recognized. The latter concentration closely agrees with the threshold previously found by Richter for rats.

Gastric motility.—The motility and tone of the empty stomach of the dog were inhibited by stretching the rectum with pressure of 20 to 48 mm. Hg. (32). Recovery usually occurred while the pressure was maintained. Undiluted gall bladder bile when placed in the rectum inhibited hunger contractions but normal saline or ten per cent glucose did not. Youmans, Meek & Herrin (33) also observed gastric inhibition from colonic distention and obtained evidence that the splanchnics were the sole efferents. Distention of the gall bladder by Brush & Patterson (34) with pressures above 50 mm. Hg produced a temporary fall in gastric tone and

motility followed by hypermotility, salivation, vomiting and inhibition of respiration. Pressures above 35 mm. Hg in the upper urinary tract were found by Campbell & Patterson (35) to produce variable changes in hunger contractions. Augmentation, inhibition and vomiting were observed. Distention of the lungs of the bullfrog by Scantlebury & Patterson (36) inhibited gastric motility, but recovery promptly followed release of the pressure.

According to Uspensky (37) the application of heat or cold to the abdomen has variable effects on human gastric tone and motility, depending in part on the previous state of the stomach.

Distention of the stomach of anesthetized rabbits or cats by Wahren (38) reduced cardiac minute volume, the volume of circulating corpuscles and the plasma volume. Lumbar anesthesia blocked the afferent pathways.

In children having poor appetites, Gulliksen, Fogelberg & Kardos (39) found no pronounced deviation from the normal in hunger contractions. The contractions were more frequent but of shorter amplitude and duration and hunger periods were more frequent but of the same duration as in normal children. The duration of the active periods and duration of the incomplete tetany periods were the same in both groups. Scott, Scott & Luckhardt (40) also noted a lack of agreement between hunger contractions and hunger sensations. In man, the administration of alcohol inhibited hunger contractions but hunger sensations were more intense. Even moderate contractions produced hunger pangs, and an epigastric sensation interpreted as appetite was experienced even while the contractions were depressed.

Scott, Scott & Luckhardt (41) and Brauch (42) found no causal relation between blood sugar values and normal hunger periods for the blood sugar level remained normal during periods of gastric activity and rest. Blotner (43), however, continues to find insulin of value in malnutrition due to nervous dyspepsia, a case in which insulin hypoglycemia apparently induces hunger by augmenting hunger contractions.

Tagita (44) found that the gastric motility recorded roentgenologically from the fasting stomach closely resembled the "hunger motility" recorded by the balloon method. Interference with the secretory activity of the testes of the cock, according to Ikegami (45), decreased gastric motility but recovery followed the administration of male sex hormone, although this hormone had

no influence on normal gastric motility. The gastric inhibition obtained by repeated injections of the duodenal hormone, enterogastrone, was found by Gray & Wieczorowski (46) in some cases to result in the development of refractoriness to these injections. This refractoriness was probably due to impurities in the extracts for continued response to the hormone elaborated physiologically has repeatedly been noted. Krugly (47) observed inhibition of hunger contractions in dogs exposed to seven per cent oxygen or an atmospheric pressure of 320 to 357 mm. Hg. Inhalation of 6.5 per cent oxygen or exposure to an atmosphere corresponding to an altitude of 8000 to 9000 ft. usually delayed gastric evacuation.

According to v. Brücke & Stern (48) stimulation of the vagi of anesthetized rabbits produced either contraction or relaxation of the cardiac sphincter. The relaxing vagal fibers behaved like sympathetics, i.e., were adrenergic and yet were true parasympathetic fibers. Parasympathetic-acting (cholinergic) fibers capable of producing cardiospasm were also present in the splanchnics. Cardiospasm produced by vagal stimulation was inhibited by atropine or epinephrine but augmented by eserine, pilocarpine or acetylcholine.

Employing optical registration of intralumen pressures, Meschan, Brody & Quigley (49) obtained values in the pyloric antrum and duodenal bulb of fasting dogs of between -5 and $+90$ cm. water. Introduction of fluids or semifluids into the stomach reduced the range and frequency of pressure changes. Usually the pressure changes were sequentially related so as to produce gastric evacuation. Intragastric pressures up to a maximum of 15 cm. water were noted by Goette & Grosser (50) but usually the pressures were below 2.5 cm. Gastric evacuation occurred simultaneously with peristaltic waves and pyloric opening. Removal of the cerebellum retarded gastric evacuation, according to Kaplan (51), but a return to normal occurred during 25 to 30 days. Hislop (52) noted a marked increase in gastric tone and motility during stimulation of the anterior hypothalamus but stimulation of the posterior hypothalamus produced a transient relaxation of the pyloric antrum.

Thomas & Crider (53) and Thomas (54) observed inhibition of pyloric antral motility with a corresponding delay in evacuation when commercial peptones, intestinal contents of dogs during protein digestion, proteoses, free amino acids, or enzyme or acid

digests of casein were introduced into the upper intestine (chiefly the lower duodenum) of dogs. Results were obtained both on the empty stomach and the stomach during digestion. Since the latent period frequently was about fifteen seconds and the inhibition could not be demonstrated following vagotomy, the vagi appeared to constitute the afferent pathway. If the evacuated material were drained to the outside by a tube in the upper duodenum the receptor mechanism was kept in a state of high sensitivity and gastric peristalsis progressively increased. Sectioning the splanchnic nerves in man increased gastric motility, according to Barron (55), and shortened evacuation time. Amphetamine sulphate decreased the initial evacuation time but increased the final emptying time (56). The delay in emptying was apparently due to gastric inhibition, and the pyloric sphincter played a very minor role. Prolonged administration of massive doses of aluminum hydroxide gel by Quigley, Einsel & Meschan (57) did not significantly alter the gastric evacuation time, the histological structure of the gastric tissue or the motility of the pyloric antrum, sphincter or duodenal bulb. Salamanca (58) presented evidence to support the contention that gastric acidity is influenced less by the quality or quantity of secretion than by the rate of evacuation, particularly of solid constituents which act as secretory excitants. Nolf (59) described the gastric motility of the bird stomach and the influence of the extrinsic nerves and the "pacemaker" on this motility. The stomach, postoperatively, frequently showed spasms and delayed evacuation, resulting perhaps from pain and the liberation of histamine-like substances (60).

Gastric secretion.—The gastric contents of twenty-day chick embryos had a pH of 4.2; the corresponding value for the twenty-seven-day goose embryo was 3.15 according to Shklyar (61). In the human newborn Huhtikangas (62) found the gastric contents to be almost neutral but after 5 hours the pH was 1.4. Eyerly & Breuhaus (63) reported that the pH of aspirated material differed from values obtained by the gastric glass electrode and antral contents had a lower pH than the whole stomach contents.

Highly purified gastrin [Komarov (64)] produced gastric juice of high acidity but low in pepsin content. In the experiments of MacIntosh (65), digestion of a meal or stimulation of the vagi did not increase the histamine content of the blood, but with the latter procedure the histamine content of gastric juice was augmented

slightly above the concentration in the blood plasma; thus histamine may mediate the action of the vagi on the parietal cells. Hasegawa (66) reported an increase in gastric total acidity following splenectomy in rabbits with Pavlov pouches and a return to normal following administration of spleen extract or atropine. The mechanisms by which substances in the stomach chemically stimulate gastric secretion were analyzed by Babkin (67). The actions of histamine and insulin on gastric secretion were also considered (68). Hollander & Penner (69) have reviewed the history and development of gastric analysis procedures.

The intravenous administration of alcohol increased the volume of gastric juice, and total and free acid were lowered, according to Lolli (70), but mucus was not augmented as it is following oral administration. Chronic alcoholism, as observed by Seymour, Spies & Payne (71), reduced gastric acidity and volume but not peptic activity.

Gray & Bucher (72) obtained evidence that gastric juice consists of a parietal secretion containing 167 m. eq. of chloride, 160 m. eq. of hydrogen ion and 7 m. eq. of potassium per liter and a non-parietal secretion with an electrolyte composition essentially that of blood. Hollander (73), by the statistical method, presented further proof that pure parietal secretion is isotonic with tissue fluid and he analyzed the mechanisms by which the acidity is lowered to the normal range (74). This subject was also reviewed by Wilhelmj & Finegan (75). Wilhelmj, Finegan & Baca (76) produced and studied deviations from normal secretory curves. Welch & Comfort (77) reported on the clinical value of the test meal of Wilhelmj, Neigus & Hill.

Noble & Robertson (78) decreased the secretory response to histamine by intravenous injection of hypertonic sodium chloride or dextrose. This action of dextrose was confirmed by Day & Komarov (79) but in their investigation the inhibition against sham feeding secretion was more pronounced. However, Friedman (80) reported an increase in gastric secretion from intravenous dextrose, but he, as well as Day & Komarov, inhibited secretion with dextrose in the gut, apparently through enterogastrone action.

According to Morrison (81) neutral red is eliminated from gastric mucosa exclusively through the parietal cells and thus a test of secretory activity of these cells is afforded. Phenol red is not

absorbed from the stomach according to Penner, Hollander & Saltzman (82) and can be used as a dilution indicator in gastric analysis.

A substance extracted from urine by Gray, Wieczorowski & Ivy (83) depressed gastric secretion. It resembled enterogastrone but did not affect gastric motility. It had no gonadotropic or vasomotor reaction. The substance obtained by Culmer, Atkinson & Ivy (84, 85) was heat-stable, but that prepared by Friedman *et al.* (86) was heat-labile and it protected Mann-Williamson dogs against ulcer formation. The administration of theelin or Antuitrin-S did not modify human gastric acidity (87, 88). Sandweiss, Saltzstein & Farbman (89) also failed to modify gastric secretion with Antuitrin-S but it did protect Mann-Williamson dogs. Normal gastric juice injected into dogs usually had no effect on gastric secretion in the studies of Brunschweig *et al.* (90) but juice from subjects with pernicious anemia or cancer produced periods of achlorhydria. The active principle was heat-labile.

Gastroelectrograms obtained by Venchikov (91) showed resting values of 40 to 50 mv. and a fall during secretion to as low as 10 mv. The resting values obtained by Titaev (92) were 28 to 30 mv. in the fundus, and 14 mv. in the antrum. The values increased with feeding.

In patients with pernicious anemia, Meulengracht (93) found atrophy of the parietal and chief cells and gastritic changes of the fundus. The pyloric portion showed but slight gastritic change with normal pyloric and Brunner's glands. According to Jones & Wilkinson (94) the proteolytic activity of gastric juice from normal individuals and from subjects with pernicious anemia was equal through a pH range from 1.5 to 10.8. Goodfield, Chain & Florey (95) obtained a reticulocytogenic agent for reactive guinea pigs from the pyloric and duodenal secretions but not from the fundic region. Administration of gastric juice to pregnant rats by Wigodsky & Noble (96) failed to influence the number, size or hemoglobin content of erythrocytes of the offspring but Stasney, Higgins & Mann (97) noted an acceleration in the reduction in size and volume of developing erythrocytes and an increase in number.

Pancreatic secretion.—In dogs responding to secretin, LaBarre & Soaje-Echague (98) inhibited pancreatic secretion by warming the frontal lobes. Secretin was purified by Greengard & Ivy (99)

to such an extent that 0.014 mg. constituted an Ivy-dog unit. Agren (100) found that the molecule of secretin contains one molecule each of histidine, aspartic acid and glutamic acid and three molecules of lysine. The juice resulting from secretin stimulation displayed equal amounts of carboxy-polypeptidase and tryptic activity.

Kunitz (101) found optima for the transformation of crystalline trypsinogen into trypsin by enterokinase at pH 5.2 to 6.0, at 5°C., and a substrate concentration not in excess of 0.1 mg. per ml. Enterokinase acted as a typical enzyme, the process following the course of a catalytic unimolecular reaction: the rate of trypsin formation varied with the concentration of enterokinase and the ultimate amount of trypsin formed varied with the concentration of enterokinase. A method for purifying enterokinase from pig duodena by fractional precipitation with ammonium sulfate was given (102).

An injection of bile into the major pancreatic duct of dogs produced a prompt rise in the serum lipase, associated with pancreatitis (103).

Bile.—According to Berliner & Schoenheimer (104), cholesterol, the four stereoisomers of dihydrocholesterol, and the bile acids corresponding in structure and spatial arrangement to these sterols were antihemolytic when a hydroxyl group was at position 3 *cis* to the methyl group at carbon atom 10 and either a *trans* fusion of rings A and B or a double bond in position 5:6. Bile acids in which the spatial arrangements of the substitutions at carbon atoms 3 and 5 were opposite those of protective compounds were strongly hemolytic.

Application of heat to the liver of anesthetized dogs was found by Osborne & Goldman (105) to increase the output of bile and its fatty acid content. Irvin, Johnston & Anderson (106) observed that bile administration increased the output of all the bile fractions. In the human, the increase in the "desoxycholic acid" group was greater than that of cholic acid, and bile acids conjugated to glycine were greatly increased. In the dog, the total bile acid was increased but the concentration was not. Administration of cystamine did not augment the taurocholic acid content of bile (107), which indicates that cystamine is not changed by the organism into taurine.

Mellanby & Suffolk (108) reported that a well-fed cat can re-

synthesize two-thirds of its cholic acid in two days but during starvation no synthesis takes place. Feeding sodium dehydrocholate increased the 24-hour volume and the chloride and cholate output but cholesterol was unchanged (109). In a human with a bile fistula Jacobi, Zuckerman & Kogut (110) observed no increase above the fasting level in bile flow from a pure carbohydrate or fat diet. Equally effective in augmenting output was the administration of bile alone or a mixed diet or a high fat diet but a protein diet was twice as effective. Addition of bile to the high fat, mixed or pure carbohydrate diet augmented the output but did not influence the flow from a high protein diet. In the dog, Schmidt, Beazell, Atkinson & Ivy (111) observed moderate choleresis from a diet high in fatty acids; conjugated bile acids (Bibron and Dechacid) were next in effectiveness to bile; oxidized, unconjugated bile acids (Ketochol and Decholin) acted as hydrocholeretics. They also observed (112) that a cholic acid output of 1.2 to 1.6 gm. per day increased to 6.5 to 90 gm. when all of the bile was returned to the duodenum. While making the enterohepatic circuit 10 to 15 per cent of the cholic acid disappeared but this was rather exactly balanced by that formed endogenously and from the diet. In anesthetized rabbits Halpert (113) noted absorption of bile from the gall bladder of 0.5 cc. per hour per kilo body weight and a flow of 3.4 cc. per hour for the first two hours followed by increased flow.

In fifteen dogs with bile fistulae, Bachrach, Schmidt & Beazell (114) obtained duodenal ulcers in two cases although bile was returned to the intestine below the site of the ulcer. Exclusion of the pancreatic juice from the intestine produced an ulcer in one case out of nineteen. Almquist & Mecchi (115) found that cholic acid cures or prevents erosion of the chick gizzard lining. Dehydrocholic acid was almost as effective but desoxycholic acid was practically ineffective. Cholic acid is normally present in the gizzard and a deficiency of cholic acid or a substitute leads to necrosis. Bird, Olsen, Elvehjem & Hart (116) have confirmed Almquist's work and also noted prevention of gizzard erosion by chondroitin; the chondrosamine portion of the molecule was not effective but the glucuronic acid fraction was.

Haney, Roley & Cole (117) employed the "Bolus" method to determine the effect of bile on intestinal propulsion activity. Gall bladder bile or a solution of bile salts markedly increased propul-

sion but other constituents of bile (bile pigments, calcium, mucin or lipoids) had no effect. Bile salts may play an important role in the normal regulation of intestinal propulsion and indirectly on gastric evacuation.

Dolkart, Jones & Brown (118) presented further evidence that fatty acids play a more important role in maintaining cholesterol in solution and preventing formation of gall stones than do bile salts or bile acids. In the disintegration of gall stones by dissolving the cholesterol, Jones & Lorenz (119) found lauric and myristic acids were two to three times better solvents than other fatty acids and were forty to fifty times more effective than bile salts. Addition of bile salts to fatty acids did not increase the solvent action of the latter. Administration of ox bile led to dissolution of implanted gall stones, not by changing the pH of bile but through its cholagogue action (120).

Doubilet & Ivy (121) found the gall bladder responded optimally to cholecystokinin if the intravesical pressure were 5 to 12 cm. of bile. With pressures above 25 cm. the response was very slight. Mecholyl inhibited the gall bladder response to a fat meal according to Schube, Myerson & Lambert (122). Seager (123) observed that the frog's gall bladder contracts after the administration of cholecystokinin or crude secretin.

Cholecystectomy, according to Puestow (124), led to permanent loss of function of the sphincter of Oddi, in spite of which the ductus choledochus became dilated. Secretin, cholecystokinin, acetylcholine, physostigmine and arecolin were noted by Auer & Seager (125) to cause contraction of the exposed papillae of the pancreatic and bile ducts. Rhythmic motility associated with blushing and blanching of the papillae and the discharge of secretion were observed (126) following the injection of crude secretin.

Ashkenaz (127) observed that stimulation of the gall bladder or the right splanchnic nerve provoked contraction of the panniculus carnosus muscle.

Intestinal motility.—Youmans, Meek & Herrin (128) observed that distention of the intestine led to motor inhibition of the gut above and below the site of distention. This inhibition passed chiefly over extrinsic nerve pathways for sectioning the intrinsic paths did not modify the response; however, an effect could be obtained, probably over intrinsic nerves, if the extrinsic paths were cut. Perfusion of the guinea pig gut *in situ*, according to Dirner

(129), stimulated motility if an optimal pressure of 8 to 9 cm. water were used. Pressures below 7 cm. were insufficient and pressures above 10 cm. led to early fatigue. When a strip of rabbit duodenum was subjected to oxygen under 75 pounds pressure, Bohr & Bean (130) observed a loss of tone and motility and the development of spasms.

Franklin & Maher-Loughnan (131) and Pannhorst (132) confirmed the spiral movements of the intestine described by Carey and by Reid, Ivy & Quigley. These movements were probably produced by the "close spiral" muscle and were often independent of the longitudinal movements produced by the "long spiral" muscle.

Movements of the gut followed weak electric stimulation of the anterior hypothalamus, superchiasmic region or ventral portion of the supramammillary decussation (133). In the terminal stages of adrenal insufficiency, Cleghorn, Fowler & Wentzel (134) found that splanchnic nerve stimulation caused splanchnic vasoconstriction, but the gut did not relax. A burst of action potentials from the intestine, according to Bozler (135), accompanied each muscular movement of the gut. The records indicated that the muscle was a syncytium and the spontaneous rhythmic movements were tetanic contractions. A continuous discharge occurred during a tetanic contraction (136). Windle & Bishop (137) observed spontaneous movements in the intestine of cat embryos at about the middle of gestation.

Denervated loops of intestine exhibited a sensitization towards epinephrine but no alteration in response to ephedrine, emphetamine or cocaine (138). Employing the bolus and balloon method, Weisel, Youmans & Cassels (139) found that morphine produced a transient increase in both propulsive and nonpropulsive motility followed by high tone and complete loss of propulsive motility. Scopolamine and cyclopropane decreased the tone and motility. Divinyl oxide and ether (140), urea (141) or apomorphine (142) inhibited the intestine; acetylcholine (143) or β-methylcholine-urethane (144) augmented motor activity.

Fieschi (145) observed tonic and rhythmic contractions in isolated normal human appendices. Strong contractions followed a rapid increase in intralumen pressure. Kokas & Ludany (146) augmented motility of the villi by stimulating the vagus; splanchnic stimulation produced inhibition. "Villikinin," the hormone

which augments motility of the villi, was not liberated by introduction of glucose into the intestine (147) but was released by dilute hydrochloric acid. Glucose absorption from the duodenum was increased 12 to 30 per cent by the presence of hydrochloric acid, apparently through the increased activity of the villi. In a cross-circulation preparation (148), hydrochloric acid introduced into the duodenum of one animal augmented contraction of the villi in the second animal. Forssell (149) presented further evidence indicating autonomous motility of the gastrointestinal mucosa, modified, however, by the motor activity of the muscular wall and the nature of the contents of the gut. This mucosal motility modified propulsion and absorption of intestinal contents.

Distention of the duodenum produced vasomotor reflexes in experiments performed by Carmichael, Doupe, Harper & McSwiney (150, 151). Vasoconstriction was more pronounced in toe vessels than in the finger and the reflex could be demonstrated with a distention too slight to produce sensation.

Intestinal secretion and absorption.—Schiffrin & Nasset (152) reported a decrease in enzyme production by the jejunum during fasting; feeding produced a decrease followed by a rise. Ileal loops responded to feeding in a similar manner but fasting did not decrease enzyme production. The concentration of enzymes in duodenal contents both normally and in disease was determined by Comfort, Parker & Osterberg (153) and Myers, Free & Beams (154). Stimulation of the vagi produced secretion from Brunner's glands but not from other portions of the intestine (155). Loew, Gray & Ivy (156) failed to obtain evidence that acid in the duodenum leads to the production of a hormone (incretin) which decreases the fasting blood sugar level.

The presence of sodium chloride in concentrations not exceeding one per cent accelerated the absorption of glucose, according to Glatzel (157). Evidence was presented by Klinghoffer (158) that monoiodoacetic acid interferes with the absorption of glucose, xylose and sodium chloride by inducing severe intestinal pathology rather than by a specific action on intestinal phosphorylation.

Althausen, Stockholm & Anderson (159) observed an absorption of 26 per cent more dextrose by female rats than by male. Gonadectomy ultimately reduced the rate of absorption by females to that of normal males but did not alter the male rate. Hypophysectomy reduced absorption by 30 to 35 per cent in both

sexes; thyroidectomy and adrenalectomy reduced the absorption rate greatly and abolished the sex difference. Administration of thyroid hormone (160) markedly increased the absorption of dextrose, xylose and oleic acid. The decreased absorption of dextrose following adrenalectomy was restored to normal by sodium chloride administration (161). Barnes, Wick, Miller & MacKay (162) reported that adrenalectomy did not modify the rate of absorption of corn oil fats; however, they administered sodium chloride to their animals. Clark (163) found the rate of sodium chloride absorption reduced in the adrenalectomized rat.

Following hemorrhage to the extent of 3.2 per cent of the body weight, Van Liere, Northrup & Sleeth (164) found that dogs absorbed less distilled water but more isotonic sodium chloride than controls; however, glucose absorption was not modified. The fluid absorbed from the gut during recovery from hemorrhage was not of much assistance in restoring normal blood pressure (165). Temporary ischemia, according to Lawson & Antoncic (166), increased absorption of histamine but intestinal obstruction did not. Selye (167) noted increased absorption of epinephrine or histamine during an "alarm reaction," induced by muscular exercise or exposure to cold.

Roepke & Visscher (168) obtained evidence indicative of active osmotic work by an unknown mechanism in the process of intestinal absorption. The total osmotic pressure of intestinal contents reached values a half atmosphere below that of blood plasma even when the major solute constituents showed concentration changes opposite to those expected on the basis of simple diffusion.

In a man having three feet of small intestine (169), absorption of carbohydrate was normal but 25 per cent of the protein was lost; practically all the fat was digested but 45 per cent appeared in the feces as fatty acids. The fatty acids interfered with calcium absorption. Hamilton (170) employed radioactive isotopes to determine rates of absorption. Sodium, chloride, bromide, and iodide could be detected in the hand in three to six minutes, potassium in six to fifteen minutes and absorption of the former was complete in three hours, but of potassium not until five hours. McCance & Widdowson (171) presented evidence that the intestine has no power to regulate by excretion the amount of iron in the body and also suggested that iron, calcium and magnesium are not eliminated through the intestine.

According to Irwin *et al.* (172), the rate of absorption of fat decreases as the melting point increases above body temperature. The rate of absorption of a hydrogenated fat was found to vary inversely with the degree of oxidation. The presence of fat with carbohydrate, according to Pollack & Dolger (173), delayed the absorption of carbohydrate. Leach (174) could find no good evidence that leucocytes play an important role in the absorption of fat. Linoleic acid in the conjugated form was absorbed approximately 100 times faster than the unconjugated form according to Barnes, Miller & Burr (175). In fish, Lovern, Morton & Ireland (176) observed that fat absorption occurs directly through the mucosal epithelium and not by a lymphatic system. It accumulates in the tunica propria from which absorption may be assisted by vitamin A which is abundant in this location. Johnson & Freeman (177) found a hemolytic substance, which may be glycerol, in the intestinal lacteals during the absorption of fats. By the time the lymph emptied into the blood stream, dilution had greatly reduced the hemolytic action.

Gray & Walzer (178) observed absorption of peanut protein directly related to the rate at which it entered the intestine. Mixtures of peptone and amino acids were each absorbed in proportion to their own concentration (179). Bradley & Belfer (180) refuted the claims of Oelgvetz, and assembled evidence supporting the classical concept that protein digestion occurs largely in the gut and very slightly in the blood; the absorption of undigested food molecules is decidedly minute.

Sodium orthophosphate was readily absorbed from the dog intestine, especially from an alkaline medium. At pH 7.0 orthophosphate and glycerophosphate were absorbed at the same rate. Evidence was presented indicating that phosphate is absorbed by the capillaries as well as the lacteals (181).

Aminoethyl phosphoric ester was believed by Outhouse to occur only in malignant tissue but Colowick & Cori (182) demonstrated its presence in the intestine of the normal rabbit and pig. According to Goffart (183) the acetylcholine content of the dog intestine rises following denervation. Sullivan & Manville (184) reported a lowering of pH in the intestine and a change to acidophilic organisms from an apple diet, but this was not confirmed by Dack, Johnson & Dragstedt (185).

Colon.—Stimulation of the peripheral end of the nervi erigentes

or the central end, if one nerve were intact, increased colonic secretion (186). Stimulation of the nerves from the inferior mesenteric ganglia simultaneously with the pelvic nerve decreased the secretion, but if the former were stimulated alone there was no effect. According to Lium & Porter (187), mucus secretion by colonic explants was not influenced by digestion or starvation. Dehydration decreased secretion and any factor increasing the muscular activity of the explant increased the secretion (188). The relation of these observations to colitis was considered. Maddock & Heath (189) obtained no evidence of iron excretion by the colon.

Amino acids and higher split products of protein were claimed by Rhoads *et al.* (190) to be absorbed from the colon more rapidly than is usually reported. Doubilet & Ivy (191) obtained slight absorption of secretin but not of cholecystokinin from the colon. The property of colonic contents tc assume the pH of the blood may be utilized according to Oelgoetz (192) to determine the blood pH. If water at pH 7.2 were injected into the colon and if after 20 minutes the pH were determined, uncompensated acidosis or alkalosis could be recognized.

In a carefully controlled study of colonic motility in dogs performed by Templeton & Borkon (193), enemas of soap solution were usually effective in producing defecation. However, when motility was studied by the balloon technic and conditions were not suitable for defecation the soap enema inhibited colonic motility. Robertson (194) fed diets low in calcium and produced hypotonicity of the colon; potassium-deficient diets had a similar but less marked effect. In colons rendered roentgenologically opaque by injections of thorium dioxide, Steggerda, Gianturco & Essex (195) sometimes obtained colonic contraction, but sometimes relaxation from pitressin. Calcium salts, physostigmine, hypertonic sodium chloride or acetylcholine increased colonic tone and motility in the experiments of Wolff (196). Pitocin, pitressin, pituitrin, ephedrine or histamine decreased tone and motility, but hypertonic glucose or parathyroid extract were without effect. In man, Jackman & Bargen (197) obtained colonic inhibition from glycerol trinitrate, amyl nitrite, syntropan or trasentin, but morphine increased the tone. Papaverine inhibited the colon (198).

Stimulation of the sympathetic nerves of a rabbit's ear, in the studies of Gaddum, Jang & Kwiatkowski (199), liberated a substance which inhibited the cecum of a fowl. Youmans (200) ob-

tained evidence of sympathin liberation in quantities sufficient to inhibit innervated or denervated intestinal loops when the rectum was stimulated.

Peptic ulcer.—Pectin had a prophylactic and curative action for peptic ulcers induced by cinchophen as was indicated by the experiments of Winters, Peters & Crook (201). Although the administration of cinchophen produced ulcers in 100 per cent of the dogs receiving this substance, if pectin were given with the cinchophen the incidence of ulcer formation was reduced to eleven per cent. In Mann-Williamson dogs Fauley *et al.* (202) were unable to demonstrate a prophylactic action from aluminum hydroxide even when administered in large doses. A decrease in food intake and loss in weight developed in these animals. The aluminum probably combined with dietary phosphates to produce phosphorus deficiency and anorexia. Emery & Rutherford (203) reported that colloidal aluminum hydroxide administered to ulcer patients gave clinical relief, neutralized the secreted acid, and brought cases with marked hypersecretion under control.

Repeated injections of pitressin by Nedzel (204) gave an incidence of ulcer of 37 per cent in dogs. These ulcers apparently resulted from vascular interference with local nutrition in the gastric mucosa and may be related to certain clinical ulcers. Opper & Zimmerman (205) reported on 21 cases of intracranial lesions associated with injury to the mucosa of the upper portion of the digestive tract. In sixteen cases the lesion was located in the nuclei of the interbrain.

The blood and urine of ulcer patients contained less ascorbic acid than normal, according to the studies of Chamberlin & Perkin (206), and the administration of vitamin C lead to earlier and greater excretion of ascorbic acid in the urine of normal individuals than in the case of ulcer patients. However, no evidence was obtained of a beneficial effect from the administration of ascorbic acid to ulcer patients.

Intestinal obstruction.—Montgomery (207) obtained evidence that obstruction of the intestine does not increase secretion and thus produces a vicious circle; in an isolated duodenojejunal loop prepared in dogs, a strangulating type of obstruction (balloon) actually depressed the secretion of the stomach, pancreas, liver and duodenum. The experiments of Wangensteen & Rea (208) strikingly emphasize the injurious effects of distention in intestinal

obstruction. After ligating the esophagus and the terminal ileum, dogs lived for 36 to 57 days. At autopsy the gut was collapsed showing complete reabsorption of digestive juices. The ultimate cause of death was not determined. Evidently, the longer duration of life in these animals resulted from the prevention of air swallowing with the consequent distention, increased intraluminal pressures, accumulation of digestive secretions and decreased viability of the gut. The experiments favor the mechanical factor of distention and not the "toxic factor" as the cause of lethal issue in ileal obstruction.

Ender & Herrin (209) sectioned the upper end of the dog jejunum and closed both ends. This produced a cecum-like loop of duodenum and jejunum which was intended to be particularly adapted to the production of toxemia. The distal end of the jejunal segment was anastomosed to the stomach to decrease the loss of salts and water. Since these animals lived approximately twice as long as animals with simple jejunal obstruction, the conclusion was drawn that toxemia appeared to be less important in intestinal obstruction than demineralization and dehydration. The vagi, splanchnics and lumbar sympathetics appeared to be involved in the vomiting, anorexia and depression produced by jejunal distention for Herrin & Meek (210) found it necessary to section all of these nerves to prevent such symptoms.

Hill & O'Connell (211) claimed that no prolongation of life in dogs with high intestinal obstruction resulted from the administration of duodenal contents through an enterostomy opening below the obstruction or by the administration of physiological sodium chloride by hypodermoclysis. In their investigation nothing was given orally, vomiting was rare and the immediate cause of death was not determined. Orr & Rumold (212) obtained results supporting the more commonly held concept. In dogs with jejunal obstruction the life span in animals receiving sodium chloride solution orally more than doubled the span in animals receiving water only. In the former group sufficient sodium chloride was absorbed to maintain the chloride content of blood almost at the normal level but in the latter group the chloride content was markedly below normal. In dogs with pyloric obstruction, the administration of sodium chloride solution led to a greater increase in the non-protein nitrogen content of the blood than in those receiving water only. The blood chloride was slightly below nor-

mal, the carbon dioxide-combining power of the blood did not increase, but the creatinine content of the blood was elevated in the group receiving sodium chloride.

In high intestinal obstruction Bisgard, McIntyre & Osheroff (213) obtained no consistent change in serum potassium or sodium but a marked fall in chloride developed. However, they concluded the changes in potassium played no role in the symptoms or death in high intestinal obstruction or duodenal fistula. Lambert & Driessens (214) ligated the intestine of rabbits and dogs and, in spite of a hypochloremia, observed that the chloride content of the segment above the obstruction was about six times greater than normal. Fontaine, *et al.* (215) found that the obstructed gut contained two to three times the normal amount of nitrogen. In man, intestinal obstruction tends to lower all the bases of the blood, according to Falconer, Osterberg & Bargen (216). Serum potassium fell more than sodium or calcium, apparently due to an active secretion of potassium into the gastric lumen from which it was lost by vomiting or aspiration.

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BLOOD: COAGULATION, BIOPHYSICAL CHARACTERS, AND FORMED ELEMENTS[1]

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Blood Coagulation

Recent studies continue to support the thrombin theory, according to which a coagulant (thrombin) is formed from an inactive precursor (prothrombin) through the agency of calcium salts and thromboplastic factors. Thrombin, in turn, converts fibrinogen into fibrin. The two fundamental processes are subject to a variety of specific and non-specific influences either aiding or inhibiting the respective reactions. Nolf (308) reviews old researches, emphasizing fibrinolytic processes, and concludes that clotting is merely a "preliminary step towards a proteolysis" and essentially a unitary system of reactions in which one or other phase may preponderate. A new enzyme theory (113) reconciles the views of Nolf (308) and of Eagle (90) by relegating the proteolytic ferment to a thromboplastic role.

Clotting factors: (1) *Prothrombin.*—The exact nature of prothrombin has not been elucidated but its preparations contain globulin protein which may be precipitated by dilution and acidification, or removed from plasma, etc., by colloidal adsorption. Purification is effected (378) by adsorbing on magnesium hydroxide gel and subsequently eluting with carbon dioxide, then drying, preferably by lyophile methods (cf. 121). Simple acetone precipitation suffices for standardized *in vitro* clotting studies (109). Prothrombin is not identical with complement (457). Like other plasma proteins, prothrombin is formed in the liver; this requires vitamin K (*q.v.*).

The clotting time of plasma (339, 384) or whole blood (463, cf. 340) on recalcifying in the presence of added thromboplastin, is a value which, under standardized conditions, and in compari-

[1] The literature reviewed falls mainly in the period June, 1938, to June, 1939, but an attempt has been made to unify the data into a coherent summary of the current status of blood problems.

son with normal controls, affords a relative estimate of prothrombin content. Quick's one-stage method, in skilled hands, is simple and approximates to natural conditions. Smith's two-stage method has theoretical advantages, notably (*a*) dissociation of the two clotting phases, giving specific information as to rate of prothrombin conversion and (*b*) independence of thromboplastin and antithrombin variables in the final clotting (431). The two methods have given comparable results in demonstrating low blood prothrombin levels with liver injury and obstructive jaundice (339, 362, 432), as well as in animals with bile fistulas (142). The relation to vitamin K is discussed below. Agreement is approaching *re* prothrombin disturbance in the newborn (265, 318, 341, 425, 426). The question of species differences in rate of thrombin formation (431, 433) as well as amount of prothrombin present (337) is receiving consideration. After transfusion, as with *in vitro* experiments, prothrombin increase is simply additive (255). Prothrombin values decrease rapidly in conserved blood (350). Quick's test is a sensitive index of liver dysfunction and parallels the hippuric acid test (452). There may be lowered prothrombin, without bleeding, in avitaminosis A and in a pellagra-like disease of chicks (277).

A series of preliminary communications from four or five laboratories [*J. Am. Chem. Soc.* 61 (1939)] indicates that the identification of vitamin K with the 1,4-naphthoquinones is complete. There is a color test (62), and bioassay methods have been improved (6, 9, 63, 405). Natural sources include alfalfa (for K_1), and kale, spinach, tomatoes, dried carrot tops, chestnut leaves, oat sprouts, soybean oil, and putrefied fish meal (for K_2) or casein or rice bran. Naphthoquinones are associated with bacterial pigment metabolism, e.g., phthiocol from the tubercle bacillus (114), and alimentary tract microorganisms are thought to elaborate adequate quantities of vitamin K in most animals, except perhaps in very young human infants. Bile is probably necessary to facilitate absorption of the fat-soluble vitamin. A choleic acid preparation (5) is effective without additional bile (52). The natural avitaminosis is limited to birds. A possible production in mice is reported (301). Experimental studies of vitamin K requirements and prothrombin levels have been made on chickens, dogs, rats, and humans with liver and biliary dysfunction. Current clinical trials in hemorrhagic diseases should be limited to

prothrombin deficiencies (41). Further studies are needed to establish the existence of other antihemorrhagic agents (253, 447).

Clotting Factors: (2) *Calcium salts.*—The role of calcium has been reviewed (105). Clotting depends on ionized, not bound calcium (244, 254). This can be reconciled with the action of trypsin in the presence of citrate or oxalate (113). Prothrombin activation proceeds through an intermediary calcium-cephalin-protein complex or compound (106, 108). The optimal amount (range) of calcium salt, and the anticoagulant effects of excess, have been further studied, *inter alia*, on human oxalate plasma (238). Strontium is said to restore to normal the low prothrombin values and clotting delay observed occasionally in parathyroidectomized dogs (115).

Preservation of fluidity of blood by citrate, oxalate, etc., continues to find innumerable applications to blood transfusion and collection of blood for plasma and cell separation, red corpuscle sedimentation test, biochemical analyses, etc. With the increasing use of "blood banks" (typed blood, conserved for transfusion purposes by citration and refrigeration, 104), there have been studies of the rate, manner, and degree of changes in conserved blood.

Clotting Factors: (3) *Thromboplastin* (*thrombokinase*).—The isolated phospholipid, cephalin, has powerful clot-aiding properties attributable to a direct and quantitative role in thrombin formation (108). Lipid analyses of platelets (98, 245), plasma, and tissue sources fail to reveal any significant quantitative anomalies but do suggest that the phospholipid is firmly bound to the proteins in a form which is not "available" for blood-clotting, until "mobilized" (113). Crude aqueous tissue extracts, thromboplastins, are more potent than the equivalent of their isolated phospholipids, indicating that a new thromboplastic factor has awaited identification. A similar suggestion emanates from work on plasma and serum globulins (329, 24). Howell (183) has advanced preliminary data suggestive of isolation. The analysis of Ferguson & Erickson (113) reveals a proteolytic thromboplastic enzyme analogous to crystalline trypsin. Mellanby & Pratt (280) assert that trypsin "activates thrombokinase," a reaction which can be inhibited by antitrypsin (281). Macheboeuf *et al.* have made extensive studies of protein-lipid associations, "cenapses," (259). Astrup's data (14, 15) are reviewed under antithrombic agents.

Both bound phospholipid and accessory thromboplastic factors come from plasma itself as well as from platelets, tissues (including brain, lung, placenta, and bone marrow), and secretions, [including milk, urine, and (132) saliva]. Biochemical relationships of plasma trypsin to its kinase (activator) and inhibitor (antitrypsin) have been worked out (372). Tryptic activity of lung extracts is reported (192).

Addis' idea (1911) of a "qualitative defect" in prothrombin in hemophilia is yielding to arguments in favor of a quantitative lack in the new thromboplastic plasma factor (183). *In vitro*, trypsin (plus calcium and cephalin) restores to normal the formation of thrombin from the prothrombin of hemophilic "globulin substance" (110). It is suggested that thromboplastic enzyme mobilizes the essential phospholipid (cephalin) from its normally inert protein combinations and thereby makes it available for thrombin formation.

Clot retraction has long been associated with platelets and tissue extracts (cf. 265). It may be due to the incipient proteolytic action of thromboplastic enzyme (113).

Clotting factors: (4) *Thrombin.*—A highly potent preparation (379) obtained from prothrombin (378) has been tried for local hemostasis (434). It seems able to destroy its precursor (prothrombin) *in vitro* (286). In claims that thrombin has proteolytic power for fibrin (308, 334), there is insufficient cognizance of (*a*) the solubility of fibrin (11, 75, 197) and (*b*) the probability that thromboplastic enzyme (113) is carried over in the thrombin preparation. Obscure arguments for preformed thrombin in the circulating blood (88, 237) require better understanding of thromboplastic and antithrombic factors.

Clotting factors: (5) *Fibrinogen and fibrin.*—Plasma fibrinogen is a globulin-type protein of special solubilities. It is formed chiefly in the liver. Conversion from the physical state of a disperse hydrosol to the quasi-crystalline fibrin gel is the *sine qua non* of natural blood clotting. Micelle re-orientation during this process is evidenced by refractometric change, particularly well studied by the photoelectric "coagelometer" (310) and the polarization microscope (34, 85). The isoelectric point of human fibrinogen, determined by cataphoresis, is at pH 5.4, i.e., between that of α-, β- and γ-globulins (390). A soluble fibrin (profibrin) is described (11, 75, 197). Fibrinogen preparations are usually obtained by

salting-out with neutral salts; they can be lyophilized for keeping in the dry state (112). Freedom from prothrombin is secured on keeping the lyophile preparation; ordinary preparations require initial adsorption of the plasma with magnesium hydroxide or aluminium hydroxide gels (109). Methods of estimating plasma fibrinogen are reviewed from the standpoint of clinical anomalies and relation to the red corpuscle sedimentation test (158). As an index of liver dysfunction (252), the fibrinogen level is less sensitive than that of prothrombin (452).

Protein denaturation as a clue to the changes undergone by fibrinogen in blood clotting and fibrinolysis continues to receive the attention of Wöhlisch *et al.* (76, 77, 214, 458, 459). Polarographic methods are being tried (213). The denaturing action of urea plays an important part in clot acceleration and fibrinolysis (147). Its action may be reversible (76).

The difficulty in linking fibrinolysis to true proteolysis (*v. supra*) can only mean that the enzyme factors in clotting merely achieve minor degrees of protein cleavage [Pope's "disaggregation" (332)] or perhaps an intramolecular rearrangement. Bacterial fibrinolysis (411) yields evidence of alteration in immunological specificity during the process (193). Rosenmann (356) has studied the influence of vitamins A, B_1, B_2, C, and D on clotting and fibrinolysis. The rather gross *in vitro* methods suggest that vitamin B_2 (lactoflavin) inhibits fibrinolysis over a wide pH range.

Clotting Factors: (6) *Antithrombic agents.*—Heparin is thought to originate in mast cells (445). Purified products (17, 198, 211) differ in sulfur content and hence in anticoagulant potency (198). Heparins are strongly acidic, containing mucoitin-polysulfuric, -acetic, and -glycuronic acids, together with the base glucosamine (211). Their barium salts are crystallizable. Quantitative combination occurs with basic protamines (116). This is used to neutralize and titrate heparin *in vivo*, but toxic effects, exemplified by the fall of blood pressure and hyperpnea following intravenous injection of salmine in dogs, are limitations (200). Jaques *et al.* find outpouring of heparin from the liver of dogs in peptone shock and have crystallized the barium salt from the blood in these experiments. Immediately after removal of the liver, anaphylactoid shock can be induced in the dog sensitized to alum-treated horse serum, but no heparin increase occurs in this case, and the clotting time of the blood is not prolonged (435). The fate of intravenously ad-

ministered heparin is obscure; there is none in the urine and feces and none is stored, except in the intestines (199). Pure heparin, followed by a new benzidine-heparin compound, affords the greatest prolongation of clotting time (200). These *in vivo* experiments have a bearing on the clinical use of heparin in prevention of thrombosis (302). Cinephotomicrography of blood flowing through a chamber device demonstrates the mode of protection against thrombosis to be an action of heparin in preventing agglutination and lysis of platelets (29). Heparin is also being advocated for transfusions (210) and for biochemical procedures, including the red corpuscle sedimentation test (159, 198) and pH measurements *in vivo*.

Assay of heparin preparations (15, 117) has been extended to a quantitative analysis of the effects of a number of anticoagulants (14). The data throw considerable light on the mode of action of heparin. Briefly, heparin is an "anti-thrombokinase." Kinase (thromboplastin) neutralizes heparin, but also takes part in the clotting reaction proper (*v. supra*). Anticoagulants may be adsorbed on blood proteins, their clot-hindering action being diminished (cf. pro-antithrombin, *infra*). Many clot-inhibitors resemble heparin in mode of action and in the presence of sulfur in the molecule, e.g., sulfocellulose, hermophenyl, liquoid, germanin, certain dyes (Chicago blue, chlorazol fast pink), cysteine, and possibly thiosulfate (57). Their suitability for intravenous use in animals is compared (216).

There are erroneous recent denials (16, 37, 338) of the "antiprothrombic" action of heparin. The unequivocal original experiments (Howell & Holt, 1918) showed prevention of thrombin formation from prothrombin plus calcium salts. The data are equally convincing if cephalin (107) or isolated tissue phospholipids (111) are used to accelerate prothrombin activation. Failure comes through the use of strong thromboplastins (thrombokinase or aqueous tissue extracts) and too great a delay in testing. Cephalin is a poor "neutralizer" of heparin but thromboplastins (or trypsin) readily overcome the inhibition and allow thrombin formation to proceed normally after a delay of but a minute or two (111). Even heparinized hemophilic plasma is easily clotted by trypsin plus calcium (110). The "pro-antithrombic" (antithrombin-forming) action (Howell & Holt), viz., inactivation of fully formed thrombin, seen only in the presence of some plasma constituent

(37), recently shown to be albumin (338), is abundantly confirmed by all the cited workers.

The hemorrhagic diathesis.—From data covered in this review and an extensive clinical literature, which will not be cited, a brief summary of the current state of our knowledge with respect to the so-called "bleeding tendency" will be made. Bleeding involves positive causative factors as well as failure in control. Coagulation defects are an important aspect of the latter, but the former includes special factors such as the susceptibility of capillaries to injury. Fibrinogen deficiency is an uncommon cause of bleeding, usually associated with gross liver injury. Pseudohemophilia is a fibrinogen deficit and may be hereditary. Prothrombin lack has recently leapt into prominence. It is due either to liver damage or to an inadequate supply of vitamin K, generally because of failure of intestinal absorption in biliary disorders. For calcium insufficiency to be a significant cause of hemorrhage, the diffusible serum calcium would have to fall below the lowest recorded level compatible with life. Thromboplastin defects offer the clue to the clotting delay in true hemophilia. Heparin and antithrombin increase may explain conditions such as the anaphylactoid purpuras when associated with incoagulability of the blood.

Current opinion questions whether platelets and tissue factors play as important a role in blood clotting as has been believed. Normal plasma contains all necessary factors (308), but they are not "available" to induce clotting until hemorrhage or, occasionally, intravascular disturbance has taken place. "Wetting" by foreign surfaces is an important physical factor; other physical factors are associated with changes in the colloidal stability of the plasma (27).

Role of platelets; thrombocytopenia.—The labile platelets are clearly a possible source of thromboplastin, although they contain only a small fraction of the total blood phospholipids. It is very doubtful whether they contain prothrombin. It is not known just how thromboplastin is mobilized during platelet lysis, a phenomenon which is retarded in hemophilia but normal in purpura hemorrhagica. In the latter disease there is decreased capillary resistance, even in cases with normal bleeding times (357), as shown by the tourniquet or suction test (96). When the bleeding time is prolonged, it is thought that the agglutinative plugging action of the thrombi formed by platelets is at fault, rather than

any clotting anomaly, e.g., failure to provide factors such as thromboplastin. However, there may be a quantitative defect in (*a*) the factor, possibly a thromboplastic enzyme, that promotes the clot retraction which mechanically strengthens the normal thrombus and (*b*) the adhesiveness which the presence of the platelets contributes to the clot (414). Platelet destroying drugs include benzene, sulfanilamide, sedormid, phenylhydrazine, and a questionable factor thrombocytopen obtained from purpuric (Werlhof's) spleens (416) and perhaps also from normal spleens and other tissues (415). The cytotoxic effects of anti-platelet sera are not confined to the megakaryocyte-platelet system (414).

Vitamins C, P, and T.—In scurvy (avitaminosis C, or ascorbic acid deficiency) there is diminished capillary resistance but no characteristic blood anomaly. The capillary disorder abates with successful treatment by the usual vitamin C preparations. Szent-Györgyi and colleagues in 1936 alleged that ascorbic acid failed to restore capillary resistance after removal of associated flavone glucosides (citrin-hesperidin and -eriodictin, 396), whereas these completed the cure. Contrary reports based on animal experiments were promptly forthcoming (296, 464), and Robežnieks (352) pointed out that the ubiquity of vegetable flavones made the postulate of a deficiency very unlikely. Choice of cases (127) and testing methods (31, 205) may be criticised. There does seem to be evidence of a capillary controlling factor in fruit juices and of favorable clinical results with citrin (204, 363), but a conservative evaluation must regard the case for the "P" factor (flavone) as yet unproven. There has been denial (20, 314, 357) of the existence of the dietary factor "T", obtained from sesame oil and egg yolk by Schiff & Hirschberger (367). This factor was claimed to raise the platelet count and prevent thrombocytopenia in animals on deficient diets.

Hemostatic agents.—The clinical use of hemostatic agents has advanced little since 1932, when reviewed by Gold (134). Orally, most preparations are useless (397, 398). Intravenously, they are apt to be highly dangerous. Their chief field of usefulness is local, but they often fail. Mention may be made of snake venoms (163), placental extract (24, 265), bone marrow preparations (439), thrombin spray (*v. supra*), and "globulins" (24, 329). Human "globulins" can be given subcutaneously or intravenously, but a refractory phase is apt to develop (329). Highly empirical is the

use of (*a*) an egg-white preparation (50), (*b*) plant extracts containing oxalic-acid (388), and (*c*) histidine (229). The difficulty in establishing hormonal relationships to blood clotting is exemplified in the uncertainty which still prevails with regard to the use (Birch, 1932) of ovarian extracts in hemophilia (230). The accepted hemostatic action of epinephrine has been reinvestigated and compared with ephedrine (74). Acetylcholine is said to be anticoagulant *in vitro* but not *in vivo* (468). Human anxiety states are without influence (174).

Biophysical Characters of Blood and Blood Proteins

Specific gravity.—The linear relation of specific gravity to protein content permits determinations of the latter from data obtained by falling drop (215), glass bead (32), or similar techniques (39) with an accuracy that compares with refractometric (320) and other methods. Variations in specific gravity because of fluid shifts occur *inter alia* in transfusional shock (201).

Viscosity, refractive index, and surface tension.—Measurements on 2500 human sera showed deviations in these properties attributable to varying amounts and hydration of the total colloids (374). Aggregation of serum colloids and shortened blood clotting time accompany recovery from anaphylactic shock in the guinea pig, the conclusion being based on increased viscosity, lowered surface tension, and increased absorption of ultraviolet light (233). Radioactive water causes similar changes and is antianaphylactic (251). Surface tension studies made on blood treated with a variety of agents, coagulant and anticoagulant, fail to yield clear correlations with such characters as the fibrinogen and globulin contents (466, 467).

The whole question of the suspension stability of the blood colloids is ill understood, although upon it depends the full interpretation of such clinical tests as (*a*) the formol-gel test (456), (*b*) Vernes' resorcinol test (424), (*c*) the Takata-Ara reaction (47), (*d*) the Weltmann coagulation band (250), (*e*) Bendien's vanadate reaction (185), and (*f*) the colloidal gold reaction (Lange's cerebrospinal fluid test), recently applied to diluted blood serum (141). These tests seem to reflect changes in plasma globulins. Instability in water, especially referable to euglobulins, causes precipitation on dialysis (48, 49). Some "denaturing"

agents, e.g., urea (76), bile salts, and other detergents (10), appear to alter the hydrophobic-hydrophilic character of proteins and maintain the denatured protein in solution from which the original protein may be recovered. Bucher (40) has studied "perfluence" (the penetration of water into plasma colloid gels).

Methods of characterizing serum protein fractions.—Schmidt's monograph (371) embraces modern methods of studying proteins. The old thermal coagulation data have lost significance since the advent of the hypothesis that coagulation is a complex of denaturation and precipitation. There is still too little emphasis on the native state of the blood proteins and too much reliance upon artificial means of separation, which the time-honored salting-out procedures continue to dominate (346, 353). Proteins so obtained are used in studies of (*a*) viscosity (101), (*b*) ultraviolet absorption (179), (*c*) potentiometric titration curves (179), (*d*) area of Langmuir surface films (181), and (*e*) biochemical composition (227, 260). Centrifugal or other separation, after dilution and presumptive buffering of the pH at the neighborhood of the isoelectric points (*v.-infra*), is less critical than electrophoretic fractionation (54, 412). Svedberg reviews the value of the ultracentrifuge (395). Immunological methods are being extended (167, 171, 276).

Electrophoretic data.—Human serum globulin obtained cataphoretically shows precipitation maxima at approximately pH 5.1 and 6.2. Normally, migration is toward the cathode below 5.0 and toward the anode above 6.3, but in pathological sera may continue toward the cathode up to pH 6.9 (239). Tiselius has described a new apparatus (413). His earlier data for horse serum (412) define cataphoretic mobilities and the following isoelectric points (pH): albumin, 4.64; α-globulin, 5.06; β-globulin, 5.2; and γ-globulin, 6.2. Human fibrinogen is assigned 5.4 (390). Human serum (390) is similar, but rat serum (195) has only two (α- and β-) globulin fractions. The globulin "Schlieren" bands are easily modified and multiplied, especially near the isoelectric points (195), a fact suggesting that serum globulins are labile complexes (196). Amongst problems upon which this has an important bearing are questions pertaining to individuality of proteins and the significance of chemical analyses for the lipid and carbohydrate contents of artificially separated blood protein fractions. Even the globulin to albumin ratio, as determined by current salting-out

methods, must be regarded critically, notwithstanding its practical value as used clinically.

Blood proteins as a transport organ.—In view of the evidence that many blood constituents, e.g., calcium, iron, lipids, carbohydrates, and bile-pigments, are bound to the proteins, at least in part, it may very well be an important physiological function of the blood proteins to serve as a transport organ (25).

Serum protein balance.—[Weech (438).] Depletion of albumin, rather than globulin, occurs in the hypoproteinemia of dogs on low protein diets. Beef serum, chuck and liver, and eggwhite and casein effect a gradual restoration, if liver function is adequate. Gelatine is inferior. Urgently needed replacement of plasma colloid, especially in edema cases, poses interpretative problems and involves complications such as untoward reactions. Current methods include (*a*) blood transfusion, (*b*) injection of serum (128), perhaps lyophilized (4) or otherwise (404) concentrated, and (*c*) infusion of acacia (221, 258). At the "edema level" (Leiter, 1920) the serum albumin is below 2.5 to 3.0 gm. per cent, thus lowering the colloidal osmotic pressure (222) of plasma below levels adequate for normal fluid interchange. In nutritional edema, the total protein content of the subcutaneous transudate is increased to 0.02 to 0.72 per cent (average, 0.23 per cent) in dogs, or 0.1 to 0.6 per cent in man. The "permeability index" shows that albumin traverses the capillary wall somewhat more readily than globulin. There is a progressive reduction in blood volume, especially the red corpuscle volume; plasma volume levels off in twenty to thirty days in dog experiments. These volume changes necessitate correction of blood analyses, including the red corpuscle count and hemoglobin content, during periods of fluctuating protein content.

Transfusions and infusions.—Besides older direct and indirect (citrate) methods (272), there are (*a*) conservation of typed refrigerated citrated blood in "blood banks" (104, 327); (*b*) preservation with heparin (145, 228, 403), sodium polyacetylene sulfonate (294), and magnesium sulfate (2); (*c*) use of placental (43, 137, 155, 184, 319), cadaveric (249, 461), goat (19), and hemolyzed autogenous (73) bloods; and (*d*) ascitic fluid (67) and sera (*v. supra*). In addition to immuno-transfusions, special benefits are sought in the selective injection of leucocyte (161) and platelet (122) suspensions. Plasmapheresis continues as an experimental

method (444). Infusions of isotonic saline solutions with added glucose, acacia, etc., have restricted usefulness (178). Blood volume and cell studies following injection of hypertonic (30%) sodium chloride solutions have been made (351), also osmotic pressure studies (382).

Blood Volume

Although the carbon monoxide dilution method still has advocates (389), modern studies of blood volume are usually made with colloidal dyes, especially T-1824 (Evans blue) in conjunction with a spectrophotometer or photoelectric colorimeter (143). For acute animal experiments, an ingenious method consists in the introduction of a measured amount of homologous plasma *via* an arterio-venous shunt device and computation of blood volume from change in hemoglobin concentration (373). Diffusible substances, such as thiosulfate (Crandall & Anderson, 1934), permit of estimation of total "available fluid." In simultaneous estimations, the blood volume of dogs is found to be a function of the available fluid volume, both being maintained at an equilibrium level characteristic of the individual, sex, and age (144). Space limitation precludes mention of current applications of blood volume measurements.

Ultramicroscopic Particles

There is further support for the modern view that the tiny plasma particles (hemokonia), best seen by dark-field illumination, are fatty in nature (60, 95).

The Formed Elements

The extensive morphological data collected in Downey's *Handbook of Hematology* (84) show that, whereas the definitive cell types can be clearly characterized and traced back to their ancestral elements in many instances, there is persistent failure to reach unanimity of opinion concerning (*a*) the myeloblast (pluripotent stem-cell), (*b*) the megaloblast (earliest red corpuscle precursor), (*c*) interrelationships of monocytic, lymphocytic, and myeloid cell lines, and (*d*) numerous minor hematological problems. These difficulties may be attributable partly to the inherent limitations of cytological methods and partly to the possibility

that the earlier phases of differentiation are not as hard-and-fast as later maturation processes. Technical problems are imposed by modifications associated with (*a*) species, (*b*) stage in life of the individual, and (*c*) pathological disturbances. There is increasing use of bone marrow examinations, especially sternal puncture (138, 206, 349, 440), in conjunction with established methods of evaluating the blood picture. Tissue culture has many applications (316). Recent hematological studies have been made on mesenchyme (170) and mammalian embryonic liver (289). Vital staining is reviewed, with 110 references (226). Examples of its use include the study of bone marrow reticulum cells (309) and cultured leucocytes (428). Details of karyokinesis in marrow cells are described (8). Osgood offers a scheme for the identification, classification, and histogenesis of blood and marrow cells (315).

The physiological approach revolves round the mechanisms for maintaining a balance between cell loss and cell replacement. Some destructive agents act on all cell forms, others are selective. Drugs affecting the blood cells have been reviewed (118, 236, 380); special mention may be made of benzene, phenylhydrazine, aminopyrine (including causalin and novaldin), sulfanilamide and related compounds, sedormid, and arsenicals (393). Besides a possible allergic interpretation (Biggart, 1932) of drug idiosyncrasy, the effects have been attributed and denied to true allergic states (177), relative to red corpuscles (324), white corpuscles (38, 176, 257), platelets (86), and bone marrow plasma cells (232).

Physical influences include meteorological changes (26), solar radiations (241), x-rays and radium (234), neutron bombardment (460), artificial fever (80, 453), and chilling and exercise (400). The endocrines (381, 393) are somewhat obscurely implicated, e.g., female sex hormones (173, 381), the posterior pituitary (82), the anterior pituitary (83, 119, 336), the thyroid (36, 207, 273), and possibly the parathyroid (94) and the thymus (44). Epinephrine and autonomic nervous influences might be expected to play a part in blood shifts and hence in blood cell mobilization (133, 311). White cell counts are normal in human anxiety states (174).

The influence of the vitamins is even more difficult to evaluate (446). A conservative statement may be made to the effect that certain blood dyscrasias appearing in the course of avitaminoses often resolve with specific vitamin therapy. The relations of

vitamin A and carotene to anemia (270), to regenerating rat blood (1), and to platelets (256) have been emphasized. However, their importance has been denied by Clausen (51). Vitamin B_1, thiamin, has been considered generally (359, 450) and with particular reference to iron retention in infants (375) and the anemia of alcohol addicts (30). The yeast factor effective in pernicious anemia (149, 454) is not now believed to be vitamin B_2 (riboflavin) (421), B_6 or I (125) or nicotinic acid (162, 313). Vitamin C (ascorbic acid and possibly citrin) has been considered above. Anemia in scurvy is said due to (*a*) dysfunction of blood forming tissues (223) or (*b*) faulty iron absorption because of the gastrointestinal upset and dietary deficiency (3); the effects on the reticulocyte response (12, 22, 99), leucocytes (61, 300), and platelets have been considered above. Vitamin D is an alleged aid to hemopoiesis (71, 343). Vitamin E (tocopherol) has been tested with liver extract in animals poisoned with phenylhydrazine and mercuric chloride (53) and is said to stimulate hemopoiesis (325). The suggested vitamin M is said to prevent the nutritional cytopenia of monkeys (72, 240).

Red Cells

According to Haden (153) an average normal adult male, weighing 150 pounds, has a total blood volume of five liters; a total red cell mass ("erythron") of two liters (30 cc. per kg.), containing about 700 gm. of oxyhemoglobin; five million red corpuscles per cu. mm.; a mean red corpuscle volume of 90 cu.μ; a mean cell hemoglobin content of 30.8×10^{-9} gm.; a mean cell oxyhemoglobin concentration of 34.2 per cent; a mean cell diameter of 7.7μ; and a mean cell thickness of 1.95μ. Averages of mean red corpuscle volume, mean red corpuscle hemoglobin content, and mean red corpuscle oxyhemoglobin concentration are given for cases of hyperchromic macrocytic anemia, hypochromic microcytic anemia, acholuric jaundice, and polycythemia (266). Changes in blood and bone marrow after hemorrhage in untreated animals and in those treated with iron, arsenic, or liver therapy have received detailed experimental study (124).

Erythropoiesis.—While there is some doubt whether the pathological (megaloblastic), post-fetal (normoblastic), and embryonic (primitive erythroblastic) red cell lines are truly identical, there is, in each case, a characteristic sequence of nuclear and cyto-

plasmic changes ultimately yielding the non-nucleated hemoglobiniferous erythrocyte (206).

Reticulocytes.—Differential counts of cells showing cytoplasmic reticulation after supravital staining with brilliant cresyl blue are an accepted guide [Cf. Nittis (307)] to the degree of red corpuscle regeneration (190, 275, 368). Cell size, volume, and color index are not reliable criteria of maturation. Total hemoglobin and erythrocyte counts afford the final clinical test (189). Cell counts are possible on standard stained films (369).

Red corpuscle size, volume, shape, and color, etc.—[Isaacs (188).] Diameter is best measured by optical (eriometer) methods (129, 151, 224) or planimetry (295). It is unrelated to blood groups (35) but is useful in the classification of anemias (376). Red corpuscle diameter and mean cell volume average higher in infants and small children (7). Of all indices of red corpuscle volume, the most significant is the "erythron," the total cell volume per kg. (152). Mean cell volume can be calculated in various ways, including an improved refractometric method (335). In addition to the anomalies of size (anisocytosis) and shape (poikilocytosis) present in the anemias, there is current interest in ovalocytosis (elliptical forms) (120, 278, 292, 387), in spherocytosis (swollen forms) (91, 175, 279, 465), and in sickle-cell anemia (78). Color index (which distinguishes hyper- from hypo-chromia) outranks size (contrasting macro- with micro-cytosis) in characterizing anemias.

A triaxial correlation of color index, volume index, and saturation index is advocated (219). Polychromasia and basophil stippling result from poisoning with silica (303), as well as lead (87) and other substances. McCord's (1924) aggregation test does not correlate accurately with reticulocytosis (323). Basophil aggregations may be present in 5.3 per cent of the red corpuscles of premature infants but return to normal adult levels (0.5 to 2.0 per cent) within eight days. A high percentage obtains for months in young albino rats (363).

The electrophoretic mobility of red corpuscles before and after hemolysis is lessened by serum (42).

Anemias

It is increasingly recognized that the classification of anemias (103) into hard-and-fast types must yield to consideration of

individual cases in terms of the factors known to disturb and to control the erythrocyte life cycle. In addition to broad hereditary and constitutional influences (81), there are specific factors concerned. The red cell builds up hemoglobin in its cytoplasm during the nucleated (erythroblast) stage of maturation. This requires both an adequate supply of precursor materials (444) and a definite ability to utilize them (448). Chlorosis, for instance, has long been regarded as a simple iron deficiency anemia, whereas it is difficult to explain the unresponsiveness of rare cases of pernicious anemia to specific therapy.

Iron.—The iron balance is maintained by conservation of the body's stores and control of absorption. Although histological studies (268, 393) show that iron is excreted into the gastrointestinal tract, actual balance studies prove that practically all the fecal iron is non-absorbed iron, and that alimentary elimination and the small constant renal excretion do not control iron metabolism (156, 262). In the normal adult, therefore, the sole source of hemoglobin iron is endogenous. Of course, babies need iron (186, 391), and in bleeding experiments on dogs, radioactive iron (Fe^{59}) is absorbed to meet the demands made by the anemia (156). Only in the light of iron depletion can significance attach to "availability" (e.g., the dipyridyl test) of dietary (13) and therapeutic (126, 150) iron, and to the role of chemical form in which it is supplied, e.g., ferrous *vs.* ferric (419). The question of demand also governs the part played by absorption defects associated with (*a*) avitaminoses, particularly of vitamin C (3); (*b*) achlorhydria [following gastrectomy (326)], mucin increase (165), and bile deficiencies (164); and (*c*) diarrhea (407) and other gastrointestinal disturbances (423).

The storage capacity or iron reserve of the depots, such as the liver, spleen, and bone marrow is subject to variation, especially in pathological states (444). The chief variable is the power of the liver to effect the intermediary synthesis of organic iron compounds, the hematoporphyrins, which will eventually form hemoglobin. In conditions of iron depletion in dogs and rats, the iron intake is an absolute limiting factor for new hemoglobin formation; the porphyrins are readily synthetized, but the globin (protein moiety) requires adequate precursors (157, 354). The non-hemoglobin iron of red cells (202) and serum (427) is iron in course of mobilization.

Accessory metals.—Controversy continues (393) concerning the role of other metals, e.g., copper, manganese, nickel, and zinc (330); copper, zinc, and mercury (345); and cobalt (58, 420). Dogs rendered anemic by milk feeding (333) are cured by a certain minimal amount of iron (30μg.) and of copper (2 μg.); subsequent anemia from bleeding responds poorly to 30μg. of iron alone, but with addition of 4μg. of copper rapid restoration of hemoglobin occurs. It is held, therefore, that copper is an important accessory factor and that the blood level rise during hematopoiesis indicates mobilization from liver stores which are more than adequate unless specific depletion methods are used. This conclusion is favored by some workers (360, 361) and opposed by others (333, 393). In the milk anemia of copper-depleted rats (231), iron produces little, if any, new hemoglobin; chlorophyll, protoporphyrin, or bilirubin cannot be utilized; whereas the hemoglobin rises sharply if copper is given. It is suggested that copper assists the later stages of hemoglobin synthesis.

Porphyrins.—For a general review see Thomas (408). References to porphyrin (pyrrhol) compounds as aids to hemoglobin formation are cited (231). It is thought that the body is able to synthesize the necessary porphyrins and that they are utilized from exogenous sources to an extent depending upon circumstances.

Globins.—The protein moiety is a partial limiting factor in heme-globin regeneration. The body can draw upon its tissue protein reserves but in the long run must receive adequate exogenous protein (157) or essential amino acids (354). The heme-globin linkage has been elucidated (406).

Specific maturation factors.—Castle's (1929) differentiation of "extrinsic" and "intrinsic" factors continues to receive support and elucidation (393, 421). The extrinsic factor is present in brewers' yeast, rice-polishings, eggs, milk, beef, liver, and possibly in tomatoes and spinach. It has not been identified with the known components of the vitamin-B complex. Tropical sprue may be due to deficiency in extrinsic factor (451). The intrinsic factor, hemopoietin (208), is themolabile, being destroyed at 70° to 80° C., and is not identifiable as hydrochloric acid, pepsin, rennin, lipase, trypsin, or erepsin (399). Nevertheless, it is a gastric factor, possibly an enzyme, interacting with the extrinsic factor to produce an agent, ventriculin, curative for pernicious anemia. Stom-

achs from patients with pernicious anemia and carcinoma lack hemopoietin (136, 365, 449) and hence ventriculin (449). The correlation of pernicious and other macrocytic anemias (365, 423) with lesions of the gastrointestinal tract and with achlorhydria (355) may be interpreted in terms of interference with the elaboration of hemopoietin, its interaction with extrinsic factor, or the absorption of maturing principle through the circulation to the liver. Surgical data, both experimental (18) and clinicopathological (421), are difficult to reconcile with any exact localization of the site of elaboration of hemopoietin at the pyloro-duodenal region (287). It is even suggested that a hormone arising here may control production of the intrinsic factor from the oxyntic cells of the stomach (299). Defects of liver storage, shown by loss of activity in human preparations, may not be evident in some cases of macrocytic anemia or of extensive liver disease (368). The antianemia principle circulates widely, appearing in kidney and brain (421) and even in the urine (203). Efforts to isolate and identify the liver principle are proceeding (65), and a number of possibilities have been ruled out (393). Concentration may be effected by adsorption on charcoal (norite) (383). Bioassay methods have been standardized on human cases (130, 189, 190), since the responses of laboratory animals (18) have not proved satisfactory.

A review of 150 cases of tropical sprue supports the conclusion that the blood dyscrasia is primary (394). Sprue and pernicious anemia are compared (46). In aplastic anemia the emphasis is upon structural disorganization of the bone marrow, five types of which are described (349). Achrestic (191, 448) or malignant anemia, on the other hand, is a functional failure perhaps explained (269, 462) as an inability to utilize the antianemic principle, which tests show to be present in liver and other tissues.

Polycythemia.—(393) Conditions with increased red corpuscle counts may be classified (348) as (*a*) erythrocytoses and (*b*) erythemias. Experimental polycythemia (erythrocytosis) may be induced by low oxygen tension, e.g., high altitude (422), artificial fever (321), or chemicals, especially cobalt (68). Clinical polycythemia occurs occasionally in recovery from hemorrhage and in congenital heart disease, mitral stenosis, and obstructive pulmonary conditions, all of which suggest anoxic factors. Acute erythemia is a rare and fatal disease entity (79). Chronic erythemia

(Vaquez-Osler disease) is more common, and it may run a varied course (358) of interest to the physiologist on account of the various hemopoietic reactions. The erythron (the total volume of red corpuscles) is constantly high in polycythemia vera, but not significantly changed in symptomatic polycythemia (152). Mean corpuscle volume is normal, but hemoglobin content is apt to be lowered (266). Red corpuscle fragility is affected slightly, if at all (21). Sedimentation rate is retarded, owing to the altered hematocrit ratio (377).

Experimental polycythemias respond to treatment with liver extract (69) and choline hydrochloride (68). Liver extract (271), and ascorbic acid (217) fail in clinical polycythemias and the current lines of treatment (348) continue to include bleeding, irradiation, and drugs, such as arsenic, phenylhydrazine, and acetylphenylhydrazine.

Red corpuscle destruction.—There is some evidence of increased red corpuscle destruction in pernicious anemia (293) and sprue (102). Hemolytic anemias are classified into ten types (324) and are the subject of other reviews (175, 212, 322, 409). Gripwall (146) has made a special study of congenital hemolytic jaundice; the acquired type has been reported on (344); and there is support for an hemolytic theory of icterus neonatorum (441). Hemolysins have been detected in acute hemolytic anemia (64). Chilling the body may destroy red corpuscles and produce paroxysmal hemoglobinuria (182). Whereas in these pathological states there is abundant evidence of intravascular red corpuscle disintegration and phagocytosis with subsequent digestion by reticulo-endothelial cells, it is difficult to demonstrate either of these mechanisms in operation under normal physiological conditions (194). Microscopic evidence is to be sought for in material from autopsies or biopsies (bone marrow, spleen and liver). A rise in serum bilirubin (hence in the icteric index and van den Bergh reactions) and in fecal, and perhaps in urinary, elimination of altered pigments are useful guides to the amount of hemoglobin loss.

Red corpuscle fragility test.—[Cassells (45).] The osmotic fragility varies with size and type of red cell (78, 89, 175, 402) and is not always pathognomonic even in congenital hemolytic jaundice (366). Myeloid leukemias have a higher incidence than hemolytic anemias, and other anemias are not far behind (342). Fragility measurements are most accurately designated by an

hemolytic index (148, 437). The increased fragility associated with exercise and raised body temperature go hand in hand (70).

Hemolysis.—Rabbit red cells lysed by water do not lose all their hemoglobin but retain 0.9 to 3.1 per cent. The "ghosts" retain their biconcave shape, have "membranes" impermeable to hemoglobin, and are highly resistant to passage of electrical current, so that volume concentration and hence dry weight of "fixed framework" (stroma) can be determined from conductivity measurements (129). Benzene, naphthalene, and their halogenated derivatives, and also phenanthrene accelerate saponin and bile salt hemolysis of washed erythrocytes of rabbits. Estrone and estriol inhibit; anthracene, dibenzanthracene, and benzpyrene are too insoluble to have any effect. Concentration on cell surface and the kinetics of the acceleration phenomena were studied (331). Experiments on sheep red corpuscles show a correlation of spatial configuration of certain sterols with their antihemolytic action. The hemolytic action of a series of bile acids is also somewhat related to structure (28). Effects of temperature (385) and solar ultraviolet light (66) have been investigated.

Erythrocyte sedimentation test.—[Edhem (93).] In a detailed quantitative comparison of five commonly used sedimentation methods, Ham & Curtis (159) studied the influence of technical, erythrocyte, and plasma factors. Settling of red corpuscles occurs because of their greater density and is resisted by the viscosity of the medium. Stokes's law cannot be applied mathematically without introducing empirical factors to allow for deviations from the "ideal" system, due especially to (*a*) displacement currents occasioned by large volume of corpuscles relative to plasma, (*b*) capillarity of measuring tube, and (*c*) effects of varying size and shape of corpuscles. There are studies (not cited) relating to choice of citrate, oxalates, or heparin as routine anticoagulant, the best comparisons being against controls of untreated hemophilic blood. It is questionable whether red corpuscle volume should always be adjusted to an arbitrary value such as 45% by addition or subtraction of (centrifuged) plasma. It is widely held (377) that the red corpuscle count can usually be neglected. Ovalocytosis (120), spherocytosis (175), and sickle-cell formation (78) affect sedimentation curves. The major controlling variable, as a rule, is the plasma composition, with special reference to content of

fibrinogen, and occasionally of serum globulin (159). Photographic methods of recording (246, 306) offer complete records of the sedimentation. Newer methods include use of a micropipette (218) and a simplified slide method (135).

An abnormal sedimentation rate is always secondary to alterations of certain blood constituents, many of which can be defined. Its clinical value is attested particularly as a guide to the "activity" of such chronic diseases as tuberculosis, arthritis, subacute rheumatic fever, and gonorrhea. Space precludes detailed report of current applications of the test.

White Cells

Granulopoiesis or myelopoiesis.—For a general review see Downey (84). Hematological studies identify a stem cell (distinguishable from that of the lymphocytes) which typically becomes a myeloblast, but occasionally develops directly into a promyelocyte. The bone marrow becomes the dominant site of granulocyte formation shortly before birth. Myelocytes develop, typically from myeloblasts, by elaboration of specific granules, neutrophilic, eosinophilic, or basophilic, at the expense of the ground cytoplasm. Nuclear changes follow later and afford a guide to age of cell (59) perhaps interpreted most practically in the Schilling-Arneth "hemogram" (455) in which the cells are classified as: (*a*) rounded (myelocytes); (b_1) juvenile or (b_2) staff ("stabkernige") intermediary forms; and (*c*) segmented (polymorphonuclear). The "shift to left," i.e., an increase in forms (*b*) and (*a*), is "regenerative" if (b_1) preponderates, or "degenerative" if (b_2) is prominent. Occasionally, according to Pegler, a familial anomaly occurs in which chromatin ages without nuclear segmentation (247).

Factors controlling leucocyte formation.—Plausibly, but without adequate evidence, Baumann (23) advances a complex scheme of factors alleged to control white cell production, comparable to that regulating hematopoiesis. Thus a dietary extrinsic factor, possibly the vitamin B_2 complex, is said to be elaborated in the stomach and small intestine into a principle, leucopoietin, which is absorbed into the blood stream and stored in the liver, thence to be mobilized, under nervous and hormonal influences, for stimulation of the leucopoietic organs. His powerful leucocytosis producing ex-

tracts of red and yellow marrow, blood serum, liver, and gastric and intestinal mucosae are said to differ from the bone marrow concentrates of American workers (274). The white cell blood picture is excellently reviewed (455). Leucocytosis and leukopenia express excess or defects, respectively, of the balance between white cell formation or mobilization (436), and destruction.

Leukopenias.—A primary leukopenia is postulated in contradistinction to eight types of secondary granulocytopenia, classified according to the leucopoietin theory (23). Reznikoff (347) lists four groups of causative factors: (*a*) fatigue [also chilling, (400)]; (*b*) drugs (118, 236); (*c*) menstruation; and (*d*) infection. The evidence of (*a*) and (*c*) is only presumptive (393). Treatment of agranulocytosis employs blood transfusions, pentonucleotide, and liver and bone-marrow extracts (235).

Leucocytosis.—Local injections of streptococci, silver nitrate, or egg albumin cause a temporary leukopenia, due to rapid transference of circulating leucocytes to tissue foci, followed by a leucocytosis due solely to a stimulus provided by products of tissue injury (305). Transplantation experiments show "organismal differentials" in the kind and degree of blood leucocytic response and suggest that a protein stimulant to leucocytosis is involved (33). The leucocytosis factor is different from leukotaxine (283).

Leukemias.—The difference between leukemia and leucocytosis resembles that between neoplasia (100) and hyperplasia. The difficulty in drawing the distinction from the blood picture is exemplified in the leukemoid reactions (166, 455) which are varied and numerous. The leukemias proper are classified (297) as acute (123) and chronic (243). The review of Sturgis *et al.* (393) contains numerous references to clinical and hematological aspects, biochemical studies, including achlorhydria (288), and discussions as to causative factors. Transfusion of leukemic blood has been used in a case of aminopyrin granulocytopenia (304). Urine from leukemic patients is said to contain a leucopoietic principle, perhaps specific for cell type (290).

Functions of leucocytes.—All types of leucocytes evince ameboid motility and all, with possible exception of the lymphocytes (169), are phagocytic. A positive chemotropism is present for pyogenic bacteria, dead tissues (usually), and most foreign objects. Negative tropism is seen with silicates (264). Chemotaxis studies assist

in the evaluation of drug mechanisms. Sulfanilamide, for instance, is negatively chemotropic and leucotoxic and therefore cannot owe its therapeutic action to any direct leucocytic response (55). Opsonins do not affect chemotaxis, but only phagocytosis (56). Menkin's studies of leukotaxine (282) clearly differentiate it from histamine (284) and the leucocytosis-promoting factor (283). Leukotaxine has been isolated from inflammatory sites as a crystalline product which is able to attract leucocytes and also increase capillary permeability. White cell destruction with pus formation seems to depend upon the susceptibility of leucocytes, granulocytes more than monocytes, to acid autolysis (154, 285).

Phagocytosis has been studied *in vitro* by incubating leukemic and other bloods with pyococci (169) or *Leishmania* (401). The finding, contrary to time-honored assertions, of some phagocytosis by lymphocytes (169) is a basis for technical criticism. A correlation is present between type, maturity of cells, and degree of phagocytic activity. Leucocytes have long been known to contain enzymes: proteases (442, 443), amylase, catalase, oxidase, and reductase (220). Their metabolism is receiving further study with reference to glycolysis and respiratory exchange (261), radioactive phorphorus (P^{32}) (418), and fats (429). The old theory that leucocytes aid in fat absorption from the intestines is not substantiated (242).

Eosinophils.—Human eosinophils show positive chemotropism for bacteria, peptone, and material from *Trichina spiralis* (187). Eosinophilia is still an obscure problem only vaguely related to protein reactions and allergic states (225). The clinical literature (393) continues to refer to its presence in parasitic infestations, skin diseases, allergic states, granulomas (including Hodgkin's disease), and leukemias (455). Loeffler's syndrome (140, 248) suggests a significance of eosinophilia in the diagnosis of transitory lung infiltrations, especially tuberculous. The Gordon encephalitogenic test for Hodgkin's disease is said to be due to eosinophils (139, 267, 417).

Lymphocytes.—There is a suggestion that lymphocytes may aid in detoxifying bacterial poisons (298). Jordan advances a monophyletic view of the origin of all blood cells from a "lymphocytic" type of cell during lymphoid metaplasia of the bone marrow in a case of aplastic anemia (209). Basophil granulocytes in the

marrow were thought to be abortive eosinophils, and plasma cells in the marrow and spleen were interpreted as abortive erythroblasts. The causes of lymphocytosis are listed (455). Infectious mononucleosis (410) is usually considered a lymphocytosis.

Monocytes.—Dark field studies are excellent for showing ameboid movements (430). In blood and bone marrow studies of a case of monocytosis accompanying fusospirillary (Vincent's) infection, similarities of morphology, phagocytic function, and peroxidase reaction led to the conclusion that monocytes might be related to the promyelocytes (131). Wintrobe's list (455) and the older literature (84) include rare toxic (tetrachlorethane), infectious, and leukemic causes of monocytosis.

Blood Platelets

This review has already covered the role of platelets in coagulation, thrombus formation, and purpura, and the various agents which destroy or increase platelets. Olef determines the average platelet volume to be 0.33% of the blood and the mean volume of one platelet to be 7.3 cu. μ. in normal human adults. He discusses the relation of hematocrit methods to fragility and size variations (312). Sizes and types are further classified (92). Platelet counts are said to vary during the menstrual cycle (245, 328). The dark field method of examination has again been revived (364).

Thrombocytopenia.—Lowering of the platelet count is an accompaniment of conditions interfering with their origin from megakaryocytes. Bone marrow smears obtained by sternal puncture seldom show diminished numbers, except in rare fulminating cases, but may give evidence of lessened megakaryocyte breakdown (357). Secondary thrombocytopenia (97) has identifiable causes such as toxic infections, platelet-destroying drugs such as sedormid, and possibly allergy (86). Many cases are linked with other blood dyscrasias (393). Essential thrombocytopenia (idiopathic thrombocytopenic purpura or purpura hemorrhagica of Werlhof) has interested several recent reviewers (97, 168, 180, 357). Differential diagnosis from secondary symptomatic purpuras is important in decisions for splenectomy (97). Rosenthal (357) summarizes the reasons for alleged benefits from vitamins, hormones (including liver extract), moccasin snake venom, x-rays, transfusions, and splenic surgery.

General Blood Studies

Statistical analyses show (*a*) independence of values for hemoglobin, red corpuscle count, and white cell count in 1644 simultaneous determinations on 364 infants (160); (*b*) no significant age or sex differences in white cell counts, (absolute, total, and differential) and sedimentation rates in healthy adolescents of 15 to 18 years (317). Lower hemoglobin and red corpuscle counts were frequent in a group of 160 men aged 60 to 104 years (291). Hicks presents a rather complicated graphic representation of the whole blood picture (172).

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THE LYMPHATIC SYSTEM

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Literature on the lymphatic system published between January 1, 1937 and September 1, 1939, with the exception of certain Japanese papers, forms the basis for this review. The Japanese papers, most of which represent work done at the Imperial University of Kyoto, have not been included since they deal with a wide variety of unrelated subjects and are readily available in collected volumes. Where necessary for clarity a few papers published before 1937 have been referred to. Certain definitely medical aspects of the problem of the lymphatics, particularly their relationship to specific diseases, have been omitted except in special cases.

Embryology

Sabin's (1) conception of the origin of lymphatics from previously existing endothelium has been confirmed by Clark & Clark (2, 3), who have shown clearly that in the rabbit's ear new lymphatics grow by a process of sprouting from preëxisting lymphatic endothelium. A specific system of vessels is formed, and these vessels are quite independent of connective tissue cells or spaces and of the blood vascular endothelium. In certain of their transparent chambers in rabbits' ears, Clark & Clark observed a separation of the lymphatics from their former connections, which was due to mechanical factors. These isolated lymphatics always remained specific and in most instances retained their normal appearance and reaction, their vitality, and their powers of growth. No evidence of phagocytosis by the lymphatic endothelium was ever observed.

Regional Distribution and Absorptive Activities of Lymphatics

Upper respiratory tract.—The lymphatic pathway from the nose and pharynx and from the cranium has recently been the subject of a number of anatomical and physiological investigations.

Faber (4) found no evidence of a direct communication between the subarachnoid space and the lymphatic vessels of the nasal mucosa. No lymphatics could be followed through the cribriform plate. Certain materials were observed to pass through the olfactory mucosa through rather definitely defined channels in the epithelium, and once past the epithelium the materials could then be found in lymph vessels, draining directly into the superficial and deep cervical lymph nodes, and in the connective tissue spaces of the mucosa, as well as in the tissue spaces of the perineural sheath of the filaments of the olfactory nerve.

McCarrell (5), in experiments on absorption from the nasopharynx, has used most successfully a new quantitative method for the production of an even and constant flow of cervical lymph in animals. This method involves regular passive motion of the head and is free from the complications introduced by massage, which has previously been necessary to secure lymph flow from the head region. She has shown that lymphatic absorption from the nasopharynx during nasopharyngeal perfusion with Ringer's solution is too small to be measured quantitatively, whereas perfusion with distilled water results in an extensive lymphatic absorption of fluid with subsequent dilution of the cervical lymph. She has concluded that under normal physiological conditions in anesthetized animals, lymphatic absorption of fluid from the nasopharynx probably takes place to a very slight degree only.

Type III pneumococci, virulent for rabbits and instilled into the nose and trachea, were recovered by Schulz, Warren & Drinker (6) from the regional lymph during the subsequent four-hour period. In a few instances the organisms were recovered from the blood, but at a later time. The intravenous administration of antiserum two and one half to three hours before the instillation of the organisms decreased the number of animals in which lymph or blood became positive. The total length of time in which organisms were recovered from the efferent lymphatics was also considerably reduced. The dyes, trypan blue and T-1824, appeared in cervical lymph 15 to 30 minutes after being placed in the nose of the cat and monkey, 51 to 53 minutes in the dog, and 14 minutes in the rabbit (7). No Hydrokollag, dropped into the nose, was ever found in cervical lymph. Trypan blue and T-1824 were also absorbed from the nose directly into the blood. Neither of the dyes

used nor the Hydrokollag, although left in the nose for as long as six hours, was found to pass through the cribriform plate and reach the interior of the cranium. Prussian blue, rapidly absorbed from the surface of the olfactory mucosa in mice (8), was found within two minutes in the tissue spaces, in blood and lymph vessels, in the perineural spaces of the olfactory nerve fibers, and in the subarachnoid space and pia-arachnoid membrane. Horse serum, instilled into the nose, was never detected in the cervical lymph of cats or rabbits. Egg albumin was found in the cervical lymph of both animals but serum albumin was detected in the lymph of cats only (9).

Not until twelve hours after nasal instillation were Yoffey & Sullivan (10) able to find vaccinia virus in cervical lymph of susceptible animals. The virus passed through the lymph nodes, but apparently they had no filtering action upon it. Centrifuging lymph caused the virus to come down with the lymphocytes but its relation to them is unknown. Since the virus becomes fixed in some way by the lymphocytes, and since lymphocytes are constantly leaving the nodes in large numbers, the authors believe that unless the node becomes completely disorganized, virus also must leave with the lymphocytes. On the other hand, one strain of poliomyelitis virus, the Toomey "T" strain, could not be detected in either cervical or thoracic duct lymph of monkeys by Yoffey & Drinker (11) after intranasal or intracerebral inoculation. Other strains of virus have not yet been tried.

Larsell, Veazie & Fenton (12) have shown, by means of injecting viable streptococci into the paranasal sinuses, or into the paralaryngeal lymph nodes, that the organisms reach the lungs, the liver and the spleen. The anatomic pathway must be via the paratracheal lymphatic vessels to the great veins, and thence to the right side of the heart. From here the organisms may reach the pulmonary tissue or be carried by the blood stream to other parts of the body. Most of the streptococci passing through the lungs are filtered out of the blood by the spleen and by the Kupffer cells of the liver.

Heart.—A review of the literature and further anatomical work on the lymphatics of the heart has been presented by Patek (13). In the dog the subepicardial lymphatic capillaries, containing numerous valves, form a continuous plexus which covers the whole

of each ventricle. Afferents are received from the myocardial plexus and these converge to form the drainage vessels which always accompany the blood vessels. All drainage vessels unite to form a single trunk which drains the entire heart and leaves it by passing on to the anterior surface of the pulmonary artery. The myocardial and subendocardial plexuses are composed entirely of capillaries. Drainage from these two plexuses is by means of short capillaries which pass directly to the subepicardial plexus.

Pericardium.—Some years ago Drinker & Field (14) studied absorption from the pericardial cavity of the rabbit. Stewart, Crane & Deitrick (15) have been able to demonstrate the same pathways of absorption in the pericardial cavity of man. They found that a dye of the order of molecular size of phenolsulphonphthalein entered the blood stream readily from the human pericardial cavity, presumably by way of the subepicardial capillaries. Larger molecules, such as vital red, were neither absorbed by way of these vessels nor to any appreciable extent by the lymphatics, since this dye was present in the fluid which was removed one month later.

Lungs.—Working with Indigo snakes, Gillilan & Conklin (16) found that such substances as hemoglobin and vital red were readily removed from the lung by the lymphatics. Particulate matter was removed from the lung by the same pathway, the largest particles absorbed being about 2μ in size. Phagocytosis accounted for only a minor part of the removal. The greater part passed through the lung tissues to the lymphatics in a time too short for phagocytic action to have been a factor.

Various protein solutions, horse serum, crystallized hemoglobin and crystallized egg albumin, however, injected into lung alveoli in dogs by Drinker, Warren & MacLanahan (17) were invariably detected by immunological methods in blood first and in thoracic duct lymph second.

Digestive tract.—Gray (18) has injected the subserous plexus of stomach lymphatics which was found to be very rich with extensive anastomoses between the vessels running towards the two curvatures. Over a relatively wide area on the surface of the stomach he observed a reversal of lymph flow which was brought about largely by the orientation of the valves.

Absorption of amino acids from the intestine into the capil-

laries and lymphatics was found by Bolton & Wright (19) to be in accordance with the physical law of diffusion; there was no clear evidence to indicate any selective activity on the part of the capillary or lymphatic endothelium. During the process of rapid absorption of products of peptone digestion, the concentration of amino acids in the efferent venous blood of the villus was greater than the concentration in the tissue fluid of the villus as judged by the efferent lymph, which in turn was greater than the concentration in the afferent arterial blood. This difference between the concentrations of amino acids in the efferent blood and the efferent lymph probably depended on the relative position of the blood and lymph capillaries, on the velocity of flow in each, and, further, on the dilution of the villus tissue fluid by tissue fluid from the afferent blood capillaries.

Johnson & Freeman (20) found a hemolytic agent in lacteal lymph collected near the intestine and also, in lesser concentration, in thoracic duct lymph. They suggested that the absorption of the products of fat digestion into the lymphatics instead of directly into the blood stream probably protected against hemolysis by the toxic agent. That the lacteals do not absorb all of the digested fat was pointed out by Ling (21). At the peak of fat absorption, when the fat content of the lymph was increased two-fold, the portal blood contained twenty per cent and the femoral arterial blood fifteen per cent more fat than in fasting samples. No evidence was found by Leach (22) that any type of leucocyte played an important part in the transference of fat from the epithelium to the lacteals.

Work by Dick (23), Fisher (24), and Simer (25) has confirmed the existence of omental lymphatics. Simer & Webb (26) have recently shown that after experimental adhesions have been induced between the jejunum and omentum, lymphatic anastomoses are formed as early as eight days after the operation.

Reproductive tract.—Sampson (27) has shown that the fimbriae of the uterine tube is richly supplied with lymphatics which are continuous with similar vessels in the mucosa of the distal portion of the ampulla of the tube. Drainage from the lymphatics of the fimbrial mucosa also takes place into lymph vessels in the wall of the infundibulum of the tube, and from the ovarian fimbriae into the vessels in the mesosalpinx.

Serous cavities.—The mechanism of absorption from the major serous cavities of vertebrates has been studied by Allen & Vogt (28) by means of direct observations on the absorption of suspensions. The filling of terminal subserous lymphatics is coincident with expansion and stretching of tissues in which lymphatics are situated, and lymph flow is the result of compression of lymphatics during contraction or compression of the surrounding tissue. With relaxation of subserous tissues an increase in the volume of lymphatic terminals was noted. This resulted in a difference in pressure on either side of the sero-endothelial membrane which separates the lymphatic lumen from the peritoneal cavity, and particles and solutions were "sucked" into the lumen. The principles of absorption described for lymphatics of the diaphragm were shown to apply to other serous cavities—pleural, pericardial and pleuroperitoneal cavities of lower forms.

Anesthetics which most stimulate the activity of the diaphragm produce the greatest stimulation to lymphatic absorption in normal animals and in those with either a local or spreading peritonitis (29). Inflammation retarded the absorption of the indiffusible proteins, carbohydrates and dyes, substances normally removed by the lymphatics from the peritoneal cavity and from subcutaneous tissue, whereas it tended to accelerate the absorption of the diffusible carbohydrates and dyes which are normally absorbed by the blood vascular system (30).

Joints.—In experiments designed to study the manner of absorption of mecholyl in aqueous solution from normal and certain pathological joints of cats under conditions of rest and exercise, Rhinelander, Bennett & Bauer (31) found that a certain proportion of the mecholyl, absorbed from the joints, appeared to be removed slowly by way of the subsynovial lymphatics, although the greater and more rapidly absorbed proportion of the drug was removed by the blood capillaries.

Pressure in Lymphatics and Tissue Fluid

Lymph vessels.—Lymph pressure has been measured in several different places either as end pressure or as side pressure. Rouvière & Valette (32) found the end pressure in the thoracic duct of the dog to be from 15 to 20 cm. of water, while side pressure, measured by inserting cannulae into collateral branches of the thoracic duct

or into the thoracic duct from an axillary lymphatic, was 5.8 to 6.4 cm. of water. McCarrell (33) measured the side pressure in the cervical lymphatics of dogs whose heads were being moved passively, a condition simulating normal as nearly as possible in an anesthetized animal, and found that the pressure ranged from −2.8 to +3.2 cm. of water, with the majority of the pressures falling between 0.1 and 1.4 cm. of water. Venous congestion, while causing an increased flow of lymph, was without marked effect on the cervical pressure.

The only direct measurements of pressure in lymphatic capillaries, measurements made by employing the same technique used by Landis (34) in his experiments on blood capillary pressure, are those made by Königes & Ottó (35) on the central lymph vessel of an individual villus. They found that here the lymph pressure was about 24.5 mm. of mercury.

Allen (36) has suggested that the primary function of the valves in lymphatics is to permit the establishment of negative pressure in the lymphatic terminals. His measurements demonstrated an intralymphatic pressure of from −0.5 to −3.0 cm. of water. Histologically demonstrated connective tissue attachments made possible an increased lymphatic volume during stretching of the tissue. This increase in the volume of the subserous lymphatics resulted in a relative negative pressure which was effective in "sucking" suspensions into the lymphatic lumen.

Tissue spaces.—Tissue pressure, which is of considerable interest and importance in the control of movement of fluid between blood vessels, tissue spaces and lymph has been measured directly by Burch & Sodeman (37) and by Wells, Youmans & Miller (38). Using a direct manometric method, they found the mean values for the tissue pressure at heart level in ten individuals to be between 17.9 and 37.1 mm. of water in the tissues examined. Normal tissue pressure was less than the accepted values for capillary and venular pressure. In the tightly covered muscles of the leg, tissue pressure starts at a high level and during quiet standing increases quite rapidly to values which are of the magnitude required by Starling's hypothesis effectively to oppose filtration. The leg volume increases for at least 2½ hours. Wells, Youmans & Miller say that it is quite unnecessary and unlikely, in the absence of movement, to assume that fluid leaves the leg through lymphatics during quiet standing.

Beecher (39) measured venous pressure during walking in subjects having incompetent valves of the great saphenous system. Under these conditions, the normal reabsorption of tissue fluid at the venous end of the capillary being impossible, all of the tissue fluid must be carried off by the lymphatics.

Factors Affecting Lymph Production Rate

Age.—Lymph flow was observed by Holman (40) to be about twice as great in growing animals as in mature dogs, but once maturity had been reached, there was no significant change even in very old dogs. There was found to be no significant difference in the protein content of subcutaneous lymph in different age groups. The suggestion of Drinker & Field (41) that the capillary permeability may decrease with advancing years has not been substantiated in the dog.

Lymphogagues.—According to Watkins & Fulton (42), physiological saline and water given by mouth and saline given intravenously greatly increase the thoracic duct lymph flow, while certain fluids introduced into the peritoneal cavity of the dog in amounts varying from 400 to 1,000 cc. did not cause an increase in volume of the thoracic duct lymph. Intravenous pituitrin and pilocarpine increased thoracic duct lymph flow, while diuresis induced by mercuperin was accompanied by a marked decrease in lymph flow.

Rouvière & Valette (43) found that *l*-tyrosine and the dipeptides which are formed with it were more active than the peptones in causing an increased flow of lymph of higher protein content. They suggested that the tyrosine was the active component of peptone in this respect.

Acetylcholine in certain doses caused an increased flow from the thoracic duct, most of the increased lymph coming from the intestines. By direct microscopical observation, Beznák (44) showed that the acetylcholine caused a dilatation of both precapillary arteries and the capillaries of the villi, the dilatation of the former being greater. Such a condition results in an increased lymph production. The action of the acetylcholine on the capillaries and precapillary arteries was regarded as the cause of the increased flow. Acetylcholine also increased the contraction of the villi, but this was not the cause of the increased lymph flow because, when the motion of the villi was completely paralyzed, the

drug still caused the increased lymph flow. Further work on this problem was done by Königes & Ottó (35) who made actual measurements of the blood pressure in the capillaries, capillary veins, and precapillary arteries of the intestinal villi of cats, together with the colloid osmotic pressure of the blood serum and the pressure of lymph in the central lymph vessel. They concluded that the hemodynamic and osmotic pressure conditions in the villus were such as to make filtration readily possible, and that the acetylcholine acted in the manner suggested by Beznák.

Pulse.—Parsons & McMaster (45) have shown that the pulse is influential in moving fluid into lymphatics and along them. Ears of rabbits were perfused in such a way that pulsation could be imparted to the perfusate or withheld from it at will. When pulsation was present, lymph flow was rapid, whereas without it the flow was almost negligible. Non-pulsatile perfusion led to a slight flow in ears that were becoming edematous, and to an enormous flow when it was pulsatile. Not only does the pulse have an effect on the flow of lymph, but it also greatly increases the spread of subcutaneously introduced dyes through the subcutaneous tissue (46).

Spread of Substances in Tissues and Lymphatics

Spread of dye was greatly influenced by physiological and pathological changes, which added fluid to the tissue or abstracted it. Spread was greater in the quiet, living ear than in the ear of an animal just killed. It was also considerable in the frankly edematous ears of living and dead animals, but not greater in either case than in normal quiet tissues. During the early stages of edema formation, dye spread was notably rapid. It was still greater in the ears of normal animals actively moving about, and was greatest of all in tissues subjected to moderately intermittent changes in external pressure (47).

In immature animals and in those with inactive sexual skins as well as in mature animals with unswollen sexual skins, Aykroyd & Zuckerman (48) found at autopsy that injected dye had spread very little and was mostly localized at the site of injection. In animals with swollen and edematous sexual skins, the passage of injected dye through the area was rapid.

The escape of a vital dye from the lymphatics of the ears of living mice, and its subsequent movement through normal and

pathological connective tissue, have been observed by McMaster & Parsons (49) at high magnification. According to them, the dye first appeared outside such channels as bristly, wavy lines of color which were formed by dye moving between connective tissue fibers or along them. With the onset of mild edema, such as the dye induces secondarily, the bristles disappeared and the coloring became diffuse and freely movable with the micro-probe. When edema was induced before the dye was introduced into the lymphatics, the character of its escape was wholly different. It first appeared as a colored cloud, freely movable in the edema fluid. Dehydration did not change the mode of transportation of the dye through the tissue, but merely emphasized some of the characteristics of its passage. The authors say, "It is plain that connective tissue fibers serve indirectly as pathways for the transport of substances of large molecule. We have not been able by the dye method to demonstrate the presence of any free fluid in the normal tissue of the mouse's ear."

Intermittent external pressure applied to the tissue greatly increased the spread of dye along or between the connective tissue fibers (50). According to the authors, these experiments provide evidence for the presence of a tissue matrix in the organ but not of free interstitial fluid. In tissue subjected to irritant stimuli and in frankly edematous tissue free fluid was readily demonstrated.

A superficial, intermediate and deep dermal plexus of lymphatics in the skin has been demonstrated by Forbes (51) by means of injections. The deep dermal plexus has very free anastomoses and connects with the deep fascial plexus. No evidence of independent drainage from localized areas of the skin was found.

Levin, Silvers & Berkowitz (52), using the technique of Hudack & McMaster (53), found that no typical lymphatic picture was associated with any specific skin disease. They did observe, however, that the looser the skin, the greater was the lymphatic spread and the more clearly outlined were the lymphatics. Since the skin usually becomes looser with increasing age, lymphatic spread may increase with age.

By means of injecting vital dyes intradermally, human lymphatic capillaries were rendered visible, the capillaries having been entered directly. By means of this technique McMaster (54) found that lymph flow in the arm at rest was very slight. Lymph flow

ceased in an arm or leg held down, but when a previously dependent arm or leg was raised, lymph flow became active. Lymph flow ceased in an arm subjected to partial venous obstruction, but was very active during the reactive hyperemia which followed upon release of the venous obstruction. Previously, in 1933, in experiments in which dye was injected into the skin of the resting forearm, Hudack & McMaster (53) stated that normal lymph flow was rapid even when the body was at rest.

The same technique has disclosed the fact that the skin lymphatics in regions of cardiac edema are patent, full of fluid, and much widened. There are innumerable intercommunications between them, and dye escapes from them more rapidly than from vessels of normal skin. Incompetency of the valves appeared to be the cause of the passage of dye in a retrograde direction. In regions of cardiac edema, lymph stagnates despite the fact that the lymphatics were open. In nephritic edema the lymphatic capillaries were wider than normal but not as wide as in cardiac edema. No sign of incompetency of the valves was observed, and lymph flow was considerably greater than normal even when edema fluid was accumulating (55).

Although McMaster & Parsons (49) and Clark & Clark (56) have been unable to demonstrate extracellular fluid in mammals and do not believe that it exists under normal circumstances, Maurer (57) has succeeded in collecting clear straw-colored fluid from the extracellular spaces of frog muscle. Careful histological examination showed that the capillary tubes in which the fluid was collected neither tore nor penetrated the muscle fibers, but were confined within the extracellular spaces. Chloride analyses showed that the ratio of serum chloride to extracellular fluid chloride was 0.993, with a probable error of 0.010. Erythrocyte counts of the fluid showed an average of only 265 red blood corpuscles per cubic millimeter, which further confirmed its extracellular character. The protein content of the fluid averaged 1.53 per cent as compared with serum protein of 4.23 per cent from the same animals.

In the course of their experiments Robertson & Williams (58) have confirmed the fact that freely diffusible substances such as urea, glucose and creatinine are present in approximately equal amounts in the lymph and blood plasma after their concentrations have been raised in the blood by intravenous injection.

Gray (59), in a review of the relationship of the lymphatics to cancer metastases, concludes that the mode of spread to lymph nodes is generally by means of emboli of cancer cells which are carried along in the lymph stream. Except under special conditions, cancer of its own accord does not generally stimulate new formation of lymphatics. Lymphotropic theories of cancer, as well as lymph stasis theories of its origin, are quite incorrect.

Volume of Lymph

Experiments by Abel, Hampil, Jonas & Chalian (60) have shown that within eight hours after the intravenous injection of many lethal doses of tetanus antitoxin, the amount of toxin in blood and in thoracic duct lymph has reached equilibrium. Peripheral or cervical lymph contained one half as much toxin per cubic centimeter as did thoracic duct lymph. The reverse passage of the toxin from the lymph to the blood, which occurred in certain experiments in which the animals were severely bled, has suggested a method for approximately determining the lymph volume of the closed lymphatic system of a normal resting animal. When the calculations were made on the basis of the toxin content of thoracic duct lymph, a minimum value for the lymph volume was obtained; and when the lower toxin content of the peripheral lymph was used a maximum was obtained. They felt that the true value lay between the two, but nearer the first than the second. Experimental calculations, based on this method, indicate that the lymph volume of a normal animal is roughly equal to the blood volume.

Lymphocytes and Lymph Nodes

Experimental work by Moor & Newport (61) appears to indicate that lymphocytes have some deleterious effect on bacterial toxins. The vital action of the lymphocyte seemed to be impaired by higher concentrations of pneumococcus toxin, and to a less extent by tetanus toxin. Just as the polymorphs and other phagocytic cells engulf particulate matter in the defense reaction, the lymphocytes react apparently in defense against toxins.

Yoffey & Drinker (62) present evidence to show that there is no rapid and extensive circulation of lymphocytes from blood to lymph. Their calculations, based on lymphocyte counts, indicate that out of every 30 lymphocytes entering the blood from the

lymph stream, 29 are newly formed while one has entered the lymph from the blood.

The lymph of the thoracic duct of the rabbit contains medium sized and large lymphocytes in large numbers and an occasional monocyte, the remaining cells being small lymphocytes (63). In tissue culture the small lymphocytes exhibited ameboid movement. The large lymphocytes divided by mitosis into small lymphocytes. Monocytes present in the lymph became actively phagocytic *in vitro*. Evidence is wanting that in tissue culture lymphocytes are transformed into monocytes and monocytes into fibroblasts. Tissue culture studies support the view that these cells represent independent cell types.

In areas of lymph stasis, according to Jordan & Morton (64) lymphocytes are transformed into plasma cells. This fact supports the suggestion that this phenomenon is a reaction to a concentration of metabolites and the accumulation of toxin.

McMaster & Kidd (65), using rabbits, have isolated an antiviral principle within the regional lymph nodes receiving the lymph from the skin into which vaccinia virus has been injected. Thus lymph nodes may be considered to be a source of neutralizing principle for this virus.

When all vascular connections to the popliteal nodes of dogs are severed, and one or more efferent and one or more afferent lymphatic channels remain intact, the nodes do not become infected and remain viable. Chemical analyses of lymph flowing to and from such nodes indicated that anaerobic glycolysis was one of the metabolic processes taking place in the viable node. These observations, Holman & Self (66) say, imply a nutritive function on the part of the node.

Rouvière & Valette (67) found that a lymph gland totally extirpated did not regenerate. A gland of which the largest part had been resected frequently regenerated, although the regeneration was not complete. Sections and localized resections, simple or multiple, of the lymphatic pathways were not sufficient to stop the course of lymph from regions of the organism tributary to these paths. The circulation always re-established itself in one way or another.

Blalock, Robinson, Cunningham & Gray (68) were able to produce complete lymphatic blockage in only three dogs. The operative procedures in general consisted of blocking the lym-

phatic ducts in the neck and chest, of destroying the cisterna, and of interfering with the drainage of the mesenteric lymphatics. In the dogs with complete lymphatic blockage, there was an almost complete disappearance of the lymphocytes and eosinophiles from the blood stream and the animals lost weight rapidly. At autopsy the lymphatics of the abdominal organs were markedly distended and there was an extravasation of chyle into many tissues. No lymphatico-venous communications could be demonstrated.

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THE PERIPHERAL CIRCULATION

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Certain phases of recent work on the peripheral vessels have been reviewed in detail (1 to 8). These reviews, though listed separately with their titles in the bibliography, are referred to also under their respective headings. Descriptions of methods and technic are treated similarly (9 to 25).

The physical factors concerned in the peripheral circulation.— The comprehensive review by Wezler & Böger (1) presents data on the elasticity of the arterial system, peripheral resistance, and the methods for determining peripheral resistance in man. The general theory of blood pressure is discussed with relation to rest, work, hormones, and drugs. Wiggers (26), in reviewing the dynamics of hypertension, has concluded that effective peripheral resistance, while increased in hypertension, does not necessarily correspond to the degree to which blood pressure is raised. It is suggested that the humoral agent or agents responsible for experimental and human hypertension act along the entire arterial tree, decreasing the capacity and distensibility of the aorta and larger arteries, while increasing peripheral resistance in the smaller vessels (26). Wright *et al.* (27) have described evidence to support the belief that decreased distensibility of the aorta when found in conjunction with hypertension, particularly in older subjects, supplies a mechanism whereby the economy of effort during ejection remains normal or may actually become more favorable. The left ventricle in hypertension thus maintains a quotient as good as, or even better than, that of the normal left ventricle by virtue of a large pulse pressure and in spite of an elevated diastolic pressure.

In the dog's aorta, Dow & Hamilton (28) have found that the pulse wave accelerates quite evenly from the aortic arch to the femoral artery and that the elasticity of rings cut from the aorta is consistent with such acceleration; stimulation of the vagus slows the pulse wave, presumably by changing the tone of the smooth muscle fibers in the walls of the vessels. Hamilton & Dow (29) have also described the manner in which resonance and standing

waves modify the fundamental pulse form in the aorta and large arteries of the dog.

Pulse wave velocities in the arteries of the lower extremity of man have been measured during life at various distending pressures. The elasticity curves, while showing large individual differences in young individuals, are more constant in the elderly, but the average curves of young and old individuals, both normal and hypertensive, differ only slightly (30). For isolated strips of human aortae there is some correlation between sclerosis and loss of elasticity but the latter is not entirely dependent upon the former (31); this paper also includes comparative studies on the elasticity of aortic strips, elastic tissue, collagenous fibers and smooth muscle. Hürthle (32), in testing the volume changes of surviving arteries under stretch during pulsating perfusion, has found that stretching is not proportional to change in pressure; the discrepancy varies in different arteries and in different segments of long arteries. Twitching movements may be produced in some arteries by a rising pulse and by certain drugs. Marceau (33) has postulated for the muscular coat of arteries a form of contracture, which increases the rigidity of the wall without apparent change of caliber.

Nervous control of the circulation.—The question of vasodilator impulses to the peripheral blood vessels of man has been reinvestigated and their demonstration in patients with Raynaud's disease corroborated (34). Similar attempts to demonstrate the presence of sympathetic vasodilator impulses in the extremities of normal persons have usually failed (34) but Grant & Holling (35) have observed that, when warming of the body is pushed to an unusual degree, vasodilatation can be demonstrated in the proximal portions of the limb, an area in which simple loss of constrictor tone produces so little increase in blood flow that the effects of vasodilator stimulation are readily displayed. They have suggested that the defenses against a rise of body temperature consist of (*a*) dilatation of the arteriovenous anastomoses through inhibition of vasoconstrictor tone, and (*b*) with more intense heating, general dilatation of the cutaneous vessels together with sweating in response to sympathetic stimulation. The vasomotor control of the cerebral vessels has also been reviewed with emphasis on vasodilator fibers (36 to 38).

Maltesos & Schneider have studied the chronaxie and fatiga-

bility of vasodilator (39) and vasoconstrictor fibers (40). Ashkenaz (41) has described the relation of frequency and intensity of electrical stimulation of peripheral nerves to the direction and magnitude of vasomotor responses. Fleisch & Weger (42) have suggested that metabolic products affect blood flow, not only by direct action on the vessels, but also by stimulation of specific sensory nerve fibers which then reflexly induce dilatation. After perfusion of novocaine, stimulation of muscle did not increase blood flow in a number of the animals tested, but the results were not entirely consistent. Grant (166) has found in man, however, that the circulatory effects of exercise are apparently due to relatively stable metabolites and that local effects are independent of the sympathetic nervous system.

Plethysmographic studies of blood flow in the fingers by Burton & Taylor (43) have indicated that rhythmic mass discharges of the sympathetic system produce periodic constriction every thirty to sixty seconds simultaneously in all the digits, accompanied by cardiac acceleration and a slight rise of blood pressure. It follows that control of cutaneous circulation through the vasoconstrictor system is achieved by continuously varying fluctuation between high and low values, rather than by maintaining peripheral flow at an appropriate constant level. The arteries of muscle and kidney, according to Smith *et al.* (44), maintain their tone normally by intrinsic autonomous control; the tonic activity of the sympathetic vasomotor paths is negligible. These findings (*see also* 165, 173, 176) emphasize again the important differences in the vasomotor control of the arterioles in skin and muscle, in that spinal anesthesia produces maximal dilatation of cutaneous vessels. Even in the skin, generalizations are dangerous since regional differences exist; the cutaneous vessels of the head participate only weakly in vasomotor reactions to which the vessels of digital skin respond vigorously (45). Reflex vasoconstriction in the skin has been produced by chemical irritation of a segment of vein (46) and by distending the duodenum (47). The accumulation of metabolites in ischemic muscle during exercise is said to produce a reflex rise of blood pressure (48 to 50) which is not due to the pain produced.

Stimulation of the skin by mustard oil or ultraviolet light increases the amount of blood in the liver and in the cortex of the kidney of guinea pigs and in the kidney cortex of mice, whereas

similar stimulation of anesthetized skin has no effect, indicating that the changes are due to reflex activity of the nervous system (51). The rise of blood pressure produced by anoxemia and insulin in anesthetized dogs has been found by Ingraham & Gellhorn (52) to be caused by increased sympathetic discharges and not by epinephrine. In cats (53) the latent period of reflex vasoconstriction in response to pain ranges from 0.5 to 2.0 seconds, depending upon peripheral conditions. The central reflex time is more constant, ranging from 0.4 to 0.6 second. Summation can be obtained with stimulation of appropriate sympathetic fibers whether preganglionic or postganglionic (53).

Griffith *et al.* (54) have found that sympathectomy increases the number of open vasa vasorum in the femoral artery of the rat. In cats, Hinsey *et al.* (55) observed that preganglionic sympathectomy of the upper extremity may be followed by rapid regeneration. It is stated by Fatherree & Adson (56) that both preganglionic and postganglionic section of the sympathetic nerves in man increase the sensitivity of the digital arterioles to the intravenous injection of epinephrine to about the same degree, whereas lumbar ganglionectomy does not do so. Grant & Pearson (165) have also been unable to find any evidence that epinephrine is responsible for return of vascular tone after sympathectomy.

The carotid sinus mechanism, particularly with reference to chemoreceptors, has been reviewed in detail by Heymans & Bouckaert (3). According to Winder *et al.* (57), the chemoreceptors of the carotid sinus are excited by ischemia, thus meeting a requirement of the hypothesis that excitation results from interaction between their own metabolism and the immediate environment. Heymans & Bouckaert (58) observed in suitably denervated animals that changes in arterial pressure stimulate receptor fibers arising for the most part in mesenteric vessels and near the thoracic aorta. The centers of these reflexes are situated at least partially in the spinal cord. Their stimulation by changes in blood pressure lead to compensatory changes in vasomotor tone.

In the rabbit Boyd & McCullagh (59) found that denervation of the carotid sinuses and section of the aortic depressor nerves produce a temporary increase in blood pressure, recovery from which is believed to be due to vicarious assumption of circulatory control by other reflex mechanisms of the type mentioned above (58). In man Capps & de Takáts (60) observed that denervation

of the carotid sinus in two patients produced temporary hypertension lasting four and twelve days, respectively, followed later by postural hypotension. De Waele & de Velde (61) studied the effects of the important regulatory nerves upon the pulmonary circulation, concluding that physiological variations in the greater circulation do not ordinarily affect the pulmonary circulation. When physiological limits are passed, and particularly if the regulatory nerves are removed, the lesser circulation tends to follow passively the variations of the greater circulation.

Chemical factors in circulation.—The overlapping of nervous and chemical factors is illustrated by the findings of Gaddum & Kwiatkowski (62). In the perfused rabbit's ear, stimulation of the sympathetic nerve causes vasoconstriction and the liberation of a substance which can be detected by a colorimetric test for epinephrine. Ephedrine sensitizes the rabbit's ear to epinephrine and also increases the yield of this substance which may, by exclusion, be epinephrine. This action of ephedrine is attributed to inhibition of amine oxidase and is compared to the inhibition of choline esterase by physostigmin.

The intensity of the reaction to epinephrine depends upon age (63), previous dosage (64), and prior hemorrhage (65). Reversal of epinephrine action by ergotoxine is modified by the depth and nature of anesthesia; urethane favors this reversal (66) while barbiturate narcosis is unfavorable. For arterial rings a consistent relation between acidity and the action of epinephrine could not be established definitely; individual differences in reactions of arteries from various sources are emphasized (67). Small doses of acetylcholine are said to increase the effect of epinephrine (68), while large doses diminish reactivity (68, 69). The effects of adrenal insufficiency on the reaction to epinephrine has been studied in cats (70), rats (71), and man (72), but no general conclusions can be drawn.

Intra-arterial injections of epinephrine, acetylcholine, and mecholyl produce local effects in minute doses, while systemic effects occur only with much larger doses (73). Amphetamine sulfate, on the other hand, when injected intra-arterially, produces general effects but no marked local effects. It is suggested that the first three substances are destroyed or fixed locally by the tissues, whereas the last circulates for a considerable time (73).

Epinephrine injectes in small doses into the femoral artery

usually produces combinations of dilatation and constriction without pure dilator effects (74). It is suggested that the reaction to epinephrine in physiological doses consists of dilatation of the capillaries and constriction of the arterioles rather than reversal of capillary effects with increasing concentration (74). In anesthetized cats ascending intra-arterial doses of epinephrine produced only increasing retardation of blood flow (75). The continuous infusion of epinephrine produces in vagotomized, anesthetized dogs a vasomotor depression which is apparently due largely to afferent impulses from the carotid sinus (76).

The intravenous injection of epinephrine into human beings at a constant rate produces widely varying grades of vasoconstriction in the digits, with greater and more prolonged effect in the toes than in the fingers. The conspicuous variability of this response makes it difficult to demonstrate increased sensitivity to epinephrine in human beings (77). Normal and hypertensive subjects react to epinephrine by similar changes in systolic pressure, with slightly greater diastolic elevation in the latter group; no correlation exists between the blood pressure raising effects of local cold and epinephrine (78). Epinephrine does not prevent the vasomotor collapse and syncope produced by sodium nitrite chiefly because it merely increases arteriolar constriction without compensating for the decreased venous tone produced by nitrite (79).

The literature contains a large number of references to the physiological effects of the recently synthesized pressor drugs; these studies can only be listed (80 to 90) with brief mention of a few important principles. Though these substances all raise blood pressure the mechanism by which this effect is produced differs widely. Their intensity of action also differs in various species. Many of these compounds increase cardiac work in a striking manner, due in large part to direct stimulation of the heart and in part to increased return of blood arising from emptying of blood depots. Blood flow in many regions may remain approximately normal in spite of marked elevation of blood pressure. Crismon & Tainter (90) compared the action of sixteen sympathomimetic amines on spinal shock of cats. They concluded that the rational choice of an agent for restoring circulation in this form of shock must take in consideration both the predominant site of action and the differences of pressor potency in the normal and

abnormal animal. Pressor effects in intact animals cannot be accepted as reliable evidence of similar effects in the abnormal animal or in man suffering from circulatory failure of various types.

Other observations dealing with the circulatory effects of chemical agents include: the effects of the potassium ion on blood pressure (91, 92); the relation between plasma potassium and the action of epinephrine (93); the vasoconstrictor action of cocaine (94); the vasodilator effects of magnesium (95); the peripheral vasodilating action of prostigmin (96); the comparative depressor effects of colamine and its methyl derivatives (97); the vasomotor responses to drugs applied to the medullary region (98); and the action of epinephrine and acetylcholine on the nerve-free vessels of the human placenta (99).

Capillary pressure, capillary permeability and fluid movement.—Eichna & Bordley (100) have compared the methods of measuring capillary blood pressure in man, using the capillaries at the base of the finger nail. They concluded that the direct microinjection method is more accurate than the indirect capsule method. Studies of tissue pressure have clarified the role of this factor in fluid movement. Wells *et al.* (101) found that venous congestion raises tissue pressure in the muscles of the leg far more than subcutaneous tissue pressure. The rate of increase of leg volume during standing diminishes with time but does not cease entirely. The ratio of the final rate to the initial rate is compatible with the assumption that filtration ceases in muscles where tissue pressure increases rapidly, but continues indefinitely in the skin where tissue pressure increases very slowly (101). Contraction of muscle elevates local tissue pressure conspicuously (101, 102). The rhythmic changes of tissue pressure which occur during standing are ascribed to shifting tension between different anti-gravity muscle groups. Sodeman & Burch (103) studied the distensibility of the skin, finding it least in the lower extremities and greatest in the abdomen. As edema progresses, distensibility decreases, thus acting as a limiting factor in edema formation (103). The tissue pressure of the loose tissues of the eyelids remains low even when the tissues are quite edematous (104).

Capillary permeability in man, as measured with the pressure plethysmograph, is normal in hepatic disease, according to White & Jones (105), but patients with hyperthyroidism or myxedema

exhibited faster and slower fluid movement respectively. These differences may be due, as they mention, to vasodilatation and change in filtering area rather than to change in capillary permeability (105). The impermeability of the capillary wall to lipoids and their failure to exert a colloid osmotic pressure is confirmed (106). Although quiet standing increases the colloid osmotic pressure and the concentration of plasma protein disproportionately, this discrepancy can be explained by known effects of increasing concentration on the specific osmotic activity of serum albumin (106).

In man the intravenous administration of fluid at rates less than 20 cc. per minute produced very little cardiovascular change despite considerable increase in blood volume. At more rapid rates venous pressure rose, while the cardiac output increased as the rate of circulation increased. The venous pressure invariably returned to control level within ten to twenty-five minutes after the end of fluid administration in volumes of 1500 cc. or less. Peripheral vasodilatation during injection probably affords partial compensation (107). In cats massive infusions of isotonic solutions produced death from cardiac decompensation, with rising venous pressure, pulmonary edema, and collection of fluid in the body cavities (108).

The absence of any clear division between normal fluid balance and outspoken edema is emphasized by the observations of Molenaar & Roller (110), who found extracellular water increased by 20 to 25 per cent in certain maladies, including heart disease, even when clinically compensated. With severe injury, body cells appear to lose their semi-permeability and measurements of extracellular water become inaccurate. Diffusion from the blood stream into certain body fluids has been examined with reference to calcium, magnesium, and phosphorus (111); antitoxin (112); and creatinine, sugar, and urea (113). The view that aqueous humor and cerebrospinal fluid cannot be regarded as a dialysate received further support (113).

The flow of lymph and the diffusion of dyes in the rabbit's ear is conspicuously increased by pulsation of the blood vessels, by pulsatile perfusion, or by intermittent changes of external pressure (114, 115, 116). Fully developed edema increases the rate of lymph flow very slightly and does not hasten spread of dyes. While edema is actually forming, however, dyes spread much more

rapidly than usual (116). Pulsations in lymphatic vessels, synchronous with those of the arteries, have been recorded. In conjunction with the lymphatic valves, these transmitted pulsations apparently promote the flow of lymph when the muscles are inactive (117). The pathways of lymphatic absorption from the nasopharynx have been described and rates of absorption determined for distilled water, dyes, certain bacteria, carbon particles, and albumin (118 to 121).

The effect of anoxemia on the movement of fluid through the capillary wall is once more emphasized by the observations of Saslow (122). Perfusion of the frog's leg with acacia solution of adequate viscosity and colloid osmotic pressure is accompanied by edema formation, but the addition of ox erythrocytes to the acacia solution makes it possible to perfuse for several hours without producing edema. Horse serum delays the appearance of edema very slightly. Apparently the added erythrocytes check edema formation because their contained oxygen prevents anoxemia and consquent increase in capillary permeability. In man, Sjöstrand (123) found that the degree of reddening and edema of the skin produced by mechanical stimulation is proportional to the number of actually painful stimuli; it is concluded that irritation of individual pain endings in the skin initiate both processes. According to Luckner (124) nutritional edema in rats is not strikingly affected by the administration of vitamin B_1 except indirectly through changes in intestinal absorption. The appearance of edema could be related more directly to the type of food given. Protein deficit seems to be the chief factor, but specific amino acids may play a considerable role. Casein, glutathione, and cystin, added to a protein-poor edema-producing diet, delayed the appearance of edema. According to Aykroyd & Zuckerman (125) edema fluid removed from hyperemic and edematous sexual skin during certain phases of estrogenic stimulation contains over two per cent of protein.

Menkin (5) has reviewed the subject of inflammation and has emphasized the differences between histamine and leukotaxine, the latter being held responsible both for the increase of capillary permeability and for the migration of polymorphonuclear leukocytes in inflamed regions (126, 127). Silva & Bier (128 to 133) believe that the permeability factor and the chemotactic factor are separate, though they may be kindred substances. According

to them exudates of inflammatory origin contain significant amounts of histamine and also inhibitory substances which interfere with biological tests for histamine. The removal of histamine from exudates leaves their chemotactic activity unchanged. They observed that, in skin showing the reaction of Schwartzman, the concentration of histamine was many times that characteristic of normal skin. Duran-Reynals (135) described further observations on the effects of testicle extract on the speed with which certain dyes pass from the blood into the tissues.

From joint spaces, mecholyl is absorbed in large part through the capillaries, but in part through the lymphatics; the rate of absorption is increased by exercise and by inflammation (136). Absorption of cerebrospinal fluid is hastened by the intravenous injection of sorbitol (137) which passes only in small quantities from the blood into the cerebrospinal fluid and aqueous humor (138). According to Bedford (139), histamine does not affect the absorption of Tyrode solution from the subarachnoid space of dogs. The effects of carbon dioxide can be explained adequately by changes in the calibre of the cerebral vessels without invoking modification of the normal processes of formation and absorption of cerebrospinal fluid (140).

Arteriovenous anastomoses and veins.—The general subject of arteriovenous anastomoses has been reviewed recently (2). In the rabbit's ear, the arteriovenous anastomoses are said to dilate when depressor nerves are stimulated or when blood pressure is elevated by constricting the aorta (141).

The subject of venous pressure has also been reviewed (4); a modified direct method of determination has been described (16), and certain errors in the direct method have been pointed out (17). Bellis & Wangensteen (142) found that intestinal distention in anesthetized dogs increased venous pressure in the lower extremities. The effects of intravenous infusion on venous pressure have already been mentioned (107, 108).

Circulation time.—As measured by injection of sodium cyanide into the antecubital vein, the circulation time has been found by Stead & Kunkel (143) to be considerably longer if the injected arm is cool. The reactions are not only slower but also less intense than those obtained from the warmer arm in which more rapid peripheral circulation insures quicker washing out of the superficial veins. Therefore to obtain accurate circulation times from

the antecubital vein, it is essential to control the temperature of the injected extremity (143). Other papers deal with results obtained by various methods including lobelin (144), carbon dioxide (145), magnesium sulfate (146), methylene blue (147), ether and calcium gluconate (148). When the body is tilted from horizontal to 75°, circulation time is prolonged presumably because of venous stasis in the lower extremities (149).

Posture.—Systolic pressure in normal subjects falls slightly in successive measurements during the first ten minutes after the supine position is assumed; diastolic pressure does not change comparably (150). In the head-down position, blood pressure does not change although heart rate decreases and stroke volume increases (151). In the head-up position, pulse rate increases and cardiac output diminishes. The relation between angle of elevation and pulse rate is so close as to suggest that even small movements of blood cannot be compensated for completely by mobilization from blood depots (151). In the erect position, the cardiovascular effects of posture are increased by reactive hyperemia of the lower extremities (152), by active exercise of the arm (153), and by fever (154). In standing, even though arterial pressure does not change, water diuresis is delayed and albuminuria appears (155). It is suggested by Asmussen *et al.* (155) that standing reduces both intestinal and renal blood flow, thus explaining their observation that ingested water is not absorbed from the intestine until the recumbent position is again assumed. The electrocardiographic changes observed in subjects tilted to an angle of 65° have no relation to the induced changes of blood pressure (156). According to Mayerson & Toth (157), tilting to 75° decreases skin temperature, especially in the lower extremities, without relation to signs of syncope. Roth *et al.* (158) found, however, that digital skin temperatures increase when the extremities are dependent and decrease whey they are elevated. These discrepancies have been ascribed to differences in humidity and food intake (158).

Ischemia.—The ischemia produced by ligating the common iliac artery in rabbits elevates the histamine content of venous blood and muscle, increases the concentration of adenosin-like compounds, and increases tissue acidity (159). Maison & Hertzman (160) found no reason to believe that ischemic pain in muscle is due to potassium or lactate ions (160). Ischemia of heart muscle is followed by reactive hyperemia which is more than adequate

to make up for the circulatory deficit produced (161). Reactive hyperemia can be induced in the kidney, but differs from that in the extremity in being much less definite and more variable, owing probably to greater resting flow (162).

Blood flow through muscle.—While Anrep found the inflow of blood was diminished or arrested during contraction of muscle, Rein found inflow increased above the resting level. Bülbring & Burn (163) believe this difference of opinion to be due to several variables, including among others the duration of tetanus and the grade of vascular tone present. If tone is low, blood flow is reduced during tetanus of any duration. If tone is normal or high, blood flow is increased unless tetanus lasts less than five seconds. With very brief tetanus, inflow is diminished during contraction and increases sharply as soon as tetanus stops. Similar observations have been reported by Millikan (164) for the muscle of the cat's tongue.

Grant & Pearson (165) have called attention to the necessity for preventing return of venous blood from more distal parts of the extremity in plethysmographic studies of blood flow in the arm or forearm. When this error is avoided, blood flow through human muscle can be compared with that through the digits. Stimuli producing vasoconstriction in the skin of the digits either have no effect on blood flow through muscle or increase it. Small doses of epinephrine increase blood flow through muscle; this vasodilator response is greater after sympathectomy. Body warming increases digital blood flow, but does not increase flow through muscle. Resting blood flow through human muscle is rather slower than that recorded for animals (166).

In dogs (167), exercise increases blood flow in the femoral artery by as much as three hundred per cent. Essex *et al.* (168) have reported the effects of exercise on blood pressure, pulse rate, and coronary flow in trained dogs. The general circulatory effects of exercise in man have been compared in detail with those produced by the intravenous injection of epinephrine (169).

Cutaneous circulation.—Doupe *et al.* (170) found that systolic arterial pressure in the proximal and distal portions of a limb are equal only when blood flow is small. Peripheral vasodilatation lowers systolic arterial pressure distal to the site of maximal outflow. Thus, reflex vasodilatation by body warming, or exercise of muscle groups, reduces digital systolic pressure by 20 to 30 mm.

Hg. Deep and prolonged inspiration not only produces vasoconstriction in the digits but also reduces digital arterial pressure (170). According to Wilkins *et al.* (171) reflex vasodilatation increases blood flow in the terminal phalanges by as much as one hundred times, owing chiefly to dilatation of arteriovenous anastomoses. The maximum flow produced by reflex vasodilatation is almost as great as that produced by local heating. According to Wright & Phelps (172) maximal blood flow is produced in the lower extremity by local heating to 45°C. and by sciatic nerve block; reflex vasodilatation by body warming produces a submaximal increase.

That epinephrine reduces blood flow in the foot while increasing it in the calf and forearm is corroborated (173). Pitressin decreases both cutaneous and muscle flow (173). The fever produced by typhoid vaccine increases blood flow to the skin and reduces that to muscle (176). Average figures for blood flow to the feet of normal subjects and of patients with organic vascular diseases indicate that flow can be reduced to fifty per cent of normal before symptoms appear (174). Peripheral vasoconstriction in the extremities is reduced regularly by inhaling four to five per cent carbon dioxide, whereas inhalation of gas mixtures containing eight to ten per cent oxygen yield variable results (175), owing, it is suggested, to competition between vasoconstrictor effects of central sympathetic impulses and the dilator effects of local metabolites.

Hertzman (177) found that the richness of arterial supply to skin areas differs as follows in descending order: finger pad, ear lobe, toe pad, palm, forehead, dorsum of finger, hand and foot, forearm, knee, and tibia. That respiration, particularly deep inspiration, produces peripheral cutaneous vasoconstriction is reaffirmed (178 to 181). Inhalation of carbon dioxide increases this constriction by emphasizing the thoracic element of breathing (178). Ten deep breaths reduce skin temperature as much as complete obstruction to blood flow for three minutes. Capillary blood flow ceases for three to five seconds after a deep breath, and returns to normal in five to fifteen seconds (179). The inhalation of tobacco smoke produces a greater and more persistent drop of skin temperature than deep breathing alone (181).

Cutaneous circulation and temperature control.—Reviews dealing with changes of skin temperature (7) and the role played by

the cutaneous vessels in maintenance of body temperature (8) have recently appeared. Only direct references to the peripheral circulation can be cited here. According to Hick *et al.* (182), the oxygen saturation of venous blood from a cubital vein lies between 48 and 64 per cent in a cool environment, 54 and 70 per cent in the comfortable zone, 73 and 90 per cent in the hot dry zone, and between 81 and 93 per cent in the hot wet zone. Gagge *et al.* (183), in studies of clothed subjects, concluded that when the operative temperature is between 25° and 29°, thermal equilibrium is maintained by vasomotor regulation; above 29°, evaporative regulation sets in. Maximal vasoconstriction produces a difference of 4° to 4.5°C. between the internal tissues and skin. Winslow *et al.* (184) have suggested that it is incorrect to assume that vasoconstriction induced by cold occurs in an "all or none" manner, because they found evidence of regulative forces acting far down in the cold region. Locke (185) chilled rabbits severely and measured the time required for recovery of normal temperature as a measure of "fitness," which is defined as ability to maintain peripheral vascular tone and thereby to restore body temperature to its normal level.

Hemorrhage.—According to Silfverskiöld (186), hemorrhage increases the amount of blood in the liver capillaries of mice and reduces that in the capillaries of muscle. Brüner & Mertens (187) found that intact dogs compensate for blood loss up to twenty per cent by increase of heart rate without change in blood pressure. When the aortic nerves, carotid sinus nerves, and vagi are cut, the pulse rate remains more constant and the fall of blood pressure is proportional to the amount of blood lost, until blood pressure reaches very low levels. In such denervated animals, the blood pressure fell to 45 mm. Hg. when 15 to 25 per cent of the total blood volume was lost; this level was not reached in intact animals until 45 per cent of the blood was lost.

Pregnancy.—Burwell *et al.* (188) have reviewed the circulatory changes of pregnancy and have found them due to (*a*) reduced peripheral resistance by reason of arteriovenous communications in the placenta and (*b*) obstruction to venous return by the enlarged uterus.

Shock.—In dogs Davis & Jermstad (189) have observed that the redistribution of blood produced by histamine shock differs

from that produced by shock due to hemorrhage and trauma. According to Macdonald & Woolfe (190) the blood of cats in shock from trauma to a limb does not contain an abnormal concentration of histamine. However, in peptone shock Dragstedt *et al.* (191) found that histamine is liberated from the tissues and passes into the circulating blood. Similar results were reported by Tinel *et al.* (192). Among the other types of tissue trauma which lead to liberation of histamine are pulmonary embolism and embolism of the mesenteric arteries (193), inhalation of irritating gases (194), and occlusion of the pulmonary arterioles (195). Went & Martin (196) found the white rat resistant to histamine, choline, and acetylcholine; typical anaphylactic reactions could not be produced (196).

Sodium, potassium, and chloride of serum are not affected by traumatic shock (197, 198, 199). According to Swingle (197), cortin must be forced in the adrenalectomized animal before shock is induced if protective action is to be demonstrated. The cortical hormone is believed to act by maintaining capillary tone, and lack of the hormone predisposes to shock by reducing capillary tone (200).

Freeman *et al.* (201) have observed in dogs that total sympathectomy delays the shock produced by hemorrhage, eliminates the characteristic hemoconcentration, increases the effectiveness of transfusions, and modifies the tissue changes characteristic of shock in normal animals. Peripheral blood flow is reduced more in the normal animal than in the sympathectomized animal at corresponding levels of systemic blood pressure. The sympathectomized dogs are not able to tolerate as large hemorrhages as normal dogs, and blood pressure falls to a lower level at an earlier period. On the other hand (202), anaphylactic shock in cats is not significantly changed by sympathectomy. Lerche (203) found that the pH of arterial blood is diminished by shock produced by histamine, peptone, or narcosis of the vasomotor center.

In treating experimental shock in dogs, Mahoney (204) has found lyophilized plasma more effective than whole blood, whereas Allen (205) found blood more efficacious than separated plasma. Both agreed that acacia and saline were much less useful. Tainter *et al.* (206) have compared the pressor efficiency of sixteen sympathomimetic amines in cats with phenol shock. The catechol

and phenol ring derivatives preserved their pressor potency moderately well, but the phenyl ring compounds were ineffective, or actually reduced blood pressure.

Hypertension and renal ischemia.—The observation that in hypertensive subjects blood flow during vasodilatation is normal in the hand and foot is confirmed (207). Since the same holds true for flow through brain and through skeletal muscle and since cardiac output is normal, it seems likely that peripheral resistance is increased equally in these areas and others as well. In agreement with this concept is the observation that cardiac output is normal in experimental renal hypertension of dogs (208). Persisting hypertension by partial occlusion of the renal arteries has been extended to the rabbit (209) and the rat (210) with characteristic arteriolar lesions (210, 211) and cardiac hypertrophy (211). In the dog with renal ischemia, the carotid sinuses react normally (212) and pulmonary blood pressure remains normal (213). In agreement with earlier work, it has been found that the hypertension is not affected by sympathectomy (212) or by destruction of the spinal cord (214).

Verney & Vogt (212) found that "increased renal load," produced by high salt intake, high general diet, administration of urea, or unilateral nephrectomy, accentuates experimental hypertension (212). Katz *et al.* (215, 216) have observed that the ratio of ischemic to normal kidney tissue determines the appearance of hypertension. Normal kidney tissue apparently has the property of destroying, eliminating, or neutralizing the substance or substances arising from ischemic kidney tissue (215, 216, 217).

Evidence is accumulating to indicate that the adrenal glands play no direct part in the hypertension produced by renal ischemia (218, 219), but the earlier and opposite view of specific action is also supported (220).

Clamping the aorta above the kidneys simulates coarctation of the aorta and produces persisting hypertension (221, 222) with cardiac hypertrophy (223). Renal ischemia is held responsible for the hypertension above the aortic obstruction, and it is interesting to note that mean arterial pressure below the obstruction is thus restored almost to normal (222). Certain other modifications of Goldblatt's original method have been used successfully to produce renal ischemia and hypertension (224, 225). Still others, such as anastomosis between the renal artery and vein (226), injection

of kieselguhr into the renal artery, and repeated stimulation of the splanchnic nerve (227) have not produced significant or lasting hypertension.

The evidence that renal ischemia raises blood pressure by a humoral mechanism seems unassailable, but so far no single substance has been definitely implicated or identified in kidney extracts, blood, or urine. There is no definite evidence that tyramine is the responsible agent (212, 228, 229) even though in rats repeated injection may produce arteriolar necrosis (230). "Renin," the distinctive globulin-like pressor substance found in extracts of normal kidneys has been identified also in kidney perfusates in small amounts along with an epinephrine-like, alcohol soluble, dialyzable, heat-resistant substance (231), but renin could not be identified in the perfusates of ischemic kidneys (232). Various methods for isolation and assay of renin have been described (233 to 236). For accurate assay of kidney extracts, it is necessary to avoid tachyphylaxis (237, 238) and, if heterologous injections are used, anaphylaxis as well. Suitably spaced heterologous injections of kidney extracts (237) can produce anaphylaxis in the rabbit but apparently this danger is not so important when the dog is chosen as the test animal (239). The pressor potency of kidney extracts varies from species to species (237, 240) and in the same species according to age (241). Reactivity or sensitivity to the pressor substances in kidney extracts also varies with species (237) and, in rats, with age (241). According to Williams (242), ergotamine inhibits the pressor action of renin, but Helmer & Page (236) were unable to demonstrate any action of this type (237). Kohlstaedt *et al.* (243) described activation of dialyzed renin by blood colloids.

Suitably prepared extracts elevate blood pressure even after the spinal cord has been destroyed (240, 244) and constrict the vessels of the isolated leg (240, 244). Certain effects on the vessels and blood flow of the leg and kidney have been reported (240, 244, 245, 246). Extracts of kidneys of hydronephrotic rats are said to have greater pressor activity than similar extracts of normal kidneys (247), whereas extracts of pathological rabbit kidneys exhibit decreased pressor activity (233). Definite conclusions are impossible.

Attempts to demonstrate uniform pressor or vasoconstrictor action of the circulating blood in experimental renal hypertension

have generally failed (215, 248, 249) but according to Houssay & Taquini (250), blood from the vein of an ischemic kidney has greater constrictor action than blood from other veins. Moreover, if an ischemic kidney from one dog is grafted secondarily in the neck of a second nephrectomized dog, blood pressure rises in the second animal, whereas similar grafting of a normal kidney has little or no effect (217). The guanidine content of the blood is elevated by renal ischemia, but it bears no relation to the hypertension produced (251).

Urine produces complex mixtures of pressor and depressor effects with great individual variation and such differences in various species that no general conclusions can be drawn (252, 253, 254). Earlier observations that urine of hypertensive individuals has less depressor activity than that of normal individuals has, however, been confirmed (255). The deviation of urine from one kidney into the blood stream does not produce toxic symptoms or changes in blood pressure (256).

The hypertension produced by elevating cerebrospinal pressure has been studied further by Griffith & Roberts (257), who found that hypertension produced in the rat by intracisternal injection of kaolin is not accompanied by change in blood volume and can be produced in the absence of both adrenal glands. In the cat, a similar injection of kaolin elevates cerebrospinal pressure but produces only transient and trifling rise of blood pressure (258). Freeman & Jeffers (259) have found that the acute rise of blood pressure produced by suddenly increased intracranial pressure is conspicuously diminished by suitable sympathectomy. They conclude that sympathetic cardiac innervation plays an important role in the pathogenesis of this type of hypertension.

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THE PHYSIOLOGY OF THE SKIN

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The skin is an organ with multiple functions, and it is difficult to integrate the studies of all of these in the space available in this review. The literature has been surveyed from January, 1938, to September, 1939, but the selection of papers for review has necessarily been restricted. It is possible that in no special field of clinical medicine has as much of treatment remained on an empiric basis as in dermatology, and the need for interpretation of the pathologic physiology of the skin in man in the light of the increasing knowledge of its normal physiology is considerable. Studies of many phases of the physiology of the skin have been isolated and sporadic, and it is the reviewer's opinion that this organ offers a field for investigations of great practical value which has not been fully realized by physiologists.

In 1938 publication of the *Journal of Investigative Dermatology* was begun. The Journal shows promise of being a suitable means by which the present extremely scattered publication of work on the physiology of the skin can be somewhat centralized and by which better correlation of laboratory and clinical investigations of the skin can be accomplished.

No attempt in this review is made to include studies in the field of general allergy dealing with conditions involving antigen-antibody reactions in which the skin serves principally as a test organ. However, some data on transepidermal sensitization of the skin has been included. The physiology of vascular tissue is considered elsewhere in this volume. Some studies of the effects of radiation on the skin, and of its permeability and temperature have been covered in Volume I.

Permeability of the skin.—Increasing evidence is available that significant absorption of hormones may occur through both human and animal skin. Moore *et al.* have shown that testosterone and testosterone propionate, when applied to the human skin in a concentration of 50 mg. per ounce of ointment base, are readily absorbed, and provide adequate substitution therapy for deficiencies of internal secretion from the testes. They also found that the

application of face creams containing estradiol will stimulate mammary development in normal male guinea pigs, induce cornified vaginal estrus smears in spayed female rats, and maintain or increase the normal growth of the uterus. Salmon has demonstrated that dihydroxyestrin exerts an estrogenic effect on the vaginal mucous membrane when applied to the skin of the human female. Baer has determined the amount of ketohydroxyestrin which is necessary to induce estrus in spayed albino rats. He found that, when the hormone is applied in an oily vehicle, a minimal daily dose of three to four international units per 150 grams body weight of rat does not cause estrus until the ointment has been applied for two to three weeks. The estrogenic effect produced by this method of administration did not seem to be more lasting than when the substance was given subcutaneously. After estrus had occurred, it could not be maintained by amounts of estrogenic substance less than that required for inducing it. Baer seems to have ruled out the possibility of his test animals obtaining significant amounts of the estrogenic substance by licking the skin. It would appear that, while the skin is an efficient route for the administration of these substances, the dose cannot be controlled as closely as with subcutaneous administration. The use of hormone-containing cosmetics by normal persons is definitely inadvisable.

Kasahara has shown that vitamin B_1 is absorbed through the skin, since polyneuritis in pigeons is cured within twenty-four hours after administration of 20 mg. of the vitamin by this means. Reiss has studied the absorption of cholesterol, fatty acids, and cholesterol and glycerol esters applied to the human skin. On the basis of histologic studies he concluded that the rate of absorption was highest for cholesterol and lowest for stearic acid. The importance of such studies in increasing the efficiency of external therapy of the skin is obvious.

The effect of inflammation, and of allergic or histamine wheals on the absorption of various substances from the skin and subcutaneous tissues has been investigated by Abramson & Engel and Miller. Studies of this type are of clinical importance, and the earlier work of Kahn in the field has proven significant and stimulating. Abramson & Engel review the evidence that accumulations of intravenously injected dyestuffs and colloids occur in the skin

at sites of allergic and histamine wheals, and areas of inflammation. They studied the absorption of intracutaneous depots of dilute solution, of crystalloid and colloid dyestuffs and found that acceleration of absorption was always observed in the wheals. This also occurred with whole blood and certain blood pigments. Histamine iontophoresis was found to increase the rate of absorption of extravasated blood as well as purple blood pigments. On the other hand, Miller found that inflammation retards the absorption of horse serum globulin and crystalline egg albumin from the peritoneal cavity and subcutaneous tissue. The spread of trypan blue was retarded by inflammation, but a more diffusible dye, such as bromophenol blue, was absorbed more rapidly. Phenol red was excreted in the urine at the same rate if injected into either normal or inflamed subcutaneous tissue or the peritoneal cavity. It was concluded that inflammation tends to retard the absorption of indiffusible protein, carbohydrate, and dye substances, but accelerates the absorption of diffusible compounds. Bier & Planet describe a substance extracted from normal rabbit skin by grinding with sodium chloride solution which increases the permeability of the skin capillaries to trypan blue when injected subcutaneously. A similar effect was not noted with other rabbit tissues. The active principal was found to be thermoresistant and to be precipitated by half-saturated ammonium sulphate.

Other studies of the passage of various substances through the skin are available, and a collection of further data of this type will aid in the selection of medicaments for the skin on a more physiological basis. Roques *et al.* state that sodium thiosulphate is not absorbed through the skin from its solution, but affirm the known absorption of hydrogen sulphide, sodium hydrogen sulphide and sodium sulphide and state that the degree of absorption is in inverse ratio to the pH. Burgi has studied the absorption of carbon dioxide by the human skin. He determined the concentration of carbon dioxide in a bell jar before and after the subject's arm had remained in the jar for one hour. If the concentration of carbon dioxide were high, the skin would absorb it, whereas a low carbon dioxide tension resulted in its passage from the arm to the surrounding gas. He also found that hydrogen sulphide could be absorbed by the skin.

Various local anesthetics have previously been reported to be

effective on the intact skin when applied in an ointment vehicle, but the clinical results from their use have been generally disappointing unless considerable disturbance of continuity of the epidermis were present. Freystadtl states that cocaine, tutopaine, and novacaine C are ineffective in producing anesthesia of the intact human skin. He found alypine to be partially effective, causing some decrease in the sensitivity of the skin to cold, and reports the production of complete local anesthesia by pantocaine, procaine, and Psicaine N applied in ointment form, anesthesia ordinarily beginning after sixty to ninety minutes and lasting from two to ten hours. This report is interesting, but the results would seem to require confirmation.

Abramson *et al.* have studied further the introduction of histamine into the skin by iontophoresis, and question on the following grounds that wheals occurring in ragweed or timothy sensitivity or as a result of physical allergy are due to histamine or a readily diffusible "H-substance" of low molecular weight. After histamine has been introduced into the skin from the positive pole of galvanic current, it was found that some of the histamine could be recovered by application of the negative pole, even when the original dilution of histamine was 1:100,000. No histamine could be recovered from local reactions of the allergic type mentioned above. Abramson & Gorin found that the active principal of ragweed pollen could be introduced into the skin from either the positive or negative pole of the galvanic current. They state that molecules may pass through the skin by electrophoresis, electroosmotic flow of the liquid as a whole, and diffusion. It is thought that in some cases, as with ragweed extract, diffusion may predominate. Studies of this type are of interest as leads in studies of the nature of a possible common substance concerned in wheal reactions resulting from a wide variety of substances or from various types of physical stimulation.

Hydrogen ion concentration of the skin.—Continued interest in the possible significance of changes in the surface pH of the skin is in evidence. Blank has recently published a series of papers on this subject which are excellent. He describes his technique in detail, a glass electrode and vacuum tube potentiometer being employed. Blank confirms the work of earlier investigators indicating that the pH of the surface of the skin varies from 4.1 to 7.1.

Human females tend to show more variation in the surface pH than do males, and the average pH of females is approximately 0.5 units higher than that of males. The extensor surface of the arm is slightly more alkaline than the flexor surface, and the cubital fossa is the most acid area of the arm. The pH of the skin surface of girls show averages similar to those of female adults, while boys have a somewhat higher pH than do male adults. Marchionini has continued publication of data supporting his hypothesis that the bactericidal power of the skin is due to its low pH. He points out the known tendency of superficial infections of the skin to localize at sites in which the pH of the surface rises by reason of delayed evaporation and decomposition of sweat. While Marchionini's hypothesis finds considerable clinical support, it is not agreed that the surface bactericidal properties of skin are entirely attributable to its acidity. There can be no doubt that the skin is normally acid at its surface, and this often approaches the isoelectric point of keratin, which is pH 3.5.

The tolerance of the human skin to solutions of varying pH has been studied by Pillsbury & Shaffer. Buffered solutions were placed in small glass cups and these were inverted on the surface of the skin and kept in place for periods up to forty-eight hours. It was found that the intact normal skin is able to withstand solution varying in pH from −2 to 12.6. On abraded skin a violent reaction to acid of pH 1.2 was obtained. On normal skin, a sharp change in the response to alkali was noted between 12.6 and 12.8, dissolution of the stratum corneum occurring, with subsequent marked irritation. Alkaline buffer solutions applied to the surface of the skin showed a tendency to a fall in pH, but a rise was not noted when acid solutions were applied.

Koch has published a method of determining the alkalinity of the skin as evidenced by the time required for injected red litmus solution to reach a blue tint, and discusses the various factors involved. Dziulikowska noted that following intracutaneous injections of various substances there occurred a reduction in the skin acidity on the symmetrically opposite site of the body. The response of the skin of guinea pigs and albino rats by swelling in media of varying pH has been studied by Balassa & Emödi. A maximum swelling of 700 per cent occurred at pH 2.9 and a minimum of 200 to 270 per cent at pH 6.1. It was found that skin from

thyroidectomized animals showed marked swelling only in very acid solutions. In new born animals the maximum swelling was not noted in acid media, but became progressively evident with increasing of alkalinity.

Sensitivity of the skin.—As stated previously, no consideration of the skin as a test organ in allergic states has been attempted in this review. However, increasing evidence is available that the important clinical problem of transepidermal sensitization of the skin can be investigated in laboratory animals. The incidence of this disturbance, the best example of which in man is rhus venenata, is increasing, possibly in part due to the increasing variety of complex organic substances of possible sensitizing capacity with which the human skin is coming in contact. The effect of diet has again been considered by Vogt, and the influence of the ratio of potassium to calcium on the skin irritability of rabbits has been studied. According to this investigation, the ratio is increased on a hay-oats diet and decreased on one of cabbage, carrots, and dandelion leaves. On the former diet, a greater irritability to cantharides was noted and attributed to a probable higher ratio of potassium to calcium in the skin. Whether this and similar earlier reports justify the administration of calcium in large amounts to humans with skin sensitivity, the reviewer has been unable to determine.

It has been shown by Ginsberg *et al.* that a small percentage of guinea pigs may be sensitized to ragweed by painting the skin with an ether extract. On continued painting of the skin, about half of the sensitized pigs became desensitized, and the writers point out that this phenomenon is observed clinically in industrial workers who are initially sensitive to a manufacturing compound, and become desensitized by continued contact with it. It was found that guinea pigs, sensitized to horse serum (antigen-antibody reaction) previously, show no increased tendency to become sensitized to ragweed. After experimental cutaneous sensitization to 2, 4-dinitrochlorobenzene, the pigs were no more easily sensitized to ragweed. They comment on the differences seen microscopically in dermatitis of guinea pigs and humans and, very correctly, point out the difficulties of interpreting phenomena of cutaneous sensitization in humans in the light of experimental results in animals. Goodman has demonstrated the marked spe-

cificity of such reactions in a patient sensitive to procaine in which reaction was obtained only to compounds containing the radical $H_2N\langle\rangle COO$. Goldman has presented a short series of experiments indicating that guinea pigs subjected to artificial fever could not be made hypersensitive to applied turpentine.

Skin temperature.—Since the comprehensive review on skin temperature and its relation to the skin environment by Bazett, a few studies of interest have appeared. Mayerson & Toth find that when the subject assumes an upright position, a prompt fall in the temperature of the skin and subcutaneous tissues occurs. At room temperatures of 25 to 27°C. the change is most marked in the lower extremities and progressively less in the hands, abdomen, chest, neck, and forehead. But at high environmental temperature the changes are uniform and of the same magnitude. Mayerson & Toth believe their data is further evidence of compensatory vasoconstriction of the peripheral circulation, particularly of the extremities.

Landis *et al.* have described an oscillometric method of studying the peripheral vascular responses of the unanesthetized, warmed rabbit, and have compared determinations of the systolic blood pressure obtained in this way with those obtained by direct cannulation of the opposite auricular artery. Experiments with a number of pressor drugs are recorded, their administration always resulting in an elevated blood pressure and decreased skin temperature, with varying degrees of vasoconstriction in the rabbit's ear. The increase of peripheral resistance and the decrease of blood flow through the auricular vessels were disproportionate to the temporary hypertension which was noted. Following the administration of a suitably heated saline kidney extract, elevation of the blood pressure was obtained without decreasing peripheral blood flow, a relationship which is characteristic of certain types of hypertension observed in man. Saland has studied the effect of amphetamine (benzedrine) sulphate and cigarette smoking on the skin surface temperature in a group of patients with Parkinson's disease and with vascular disease. A drug capable of causing a peripheral vasoconstriction such as amphetamine almost constantly causes a drop in the skin surface temperature but cigarette smoking does not produce this consistently.

Hertzman described an adaptation of the photoelectric

plethysmograph as a means of comparison of the richness of the blood supply in several skin areas by means of transillumination of the subcutaneous tissues. The variations in the photoelectric units are recorded, after amplification, in arbitrary filter units. Finger tips and palmar surfaces were found to give the highest values.

Williams, in a careful study, has reported variation in the skin temperature response to injections of histamine in a group of persons with characteristic atopic neurodermatitis, as compared with normal persons. In persons with a normal skin the increase in the skin temperature is limited to the face and neck, while in the patients studied, an increase was also noted at the site of predilection for the eczematous eruption, namely the flexor surfaces of the knees and elbows, as well as the face. Patients with this dermatosis of apparently multiple etiology, offer an interesting and a deserving field for clinical physiologic investigation. They frequently show a "white reaction" on stroking of the skin, and the significance of this in neurodermatitis and other dermatoses has been discussed by Whitfield.

Hinsey & Phillips have studied the effect on skin temperature of a one-stage removal of the entire right sympathetic chain and of the left abdominal sympathetic chain in cats. Two months after this operation, the pads of the operated forelimbs were about three degrees Centigrade warmer than the normally innervated forelimb pads. After removal of the left thoracic sympathetic chain, less than one degree Centigrade difference in the temperature was noted. Smith noted no effect of caffeine or coffee on skin temperature and insensible perspiration.

Sweat.—Bickford has published an interesting study on local sweating in response to faradic current. The method employed consisted of application of an alcohol, castor oil, and iodine mixture to the skin, over which a finely powdered starch was blown. Sweating was indicated by the appearance of the starch-iodine blue color. With faradic stimulation, the extent of the sweating varied with the current strength employed. Sweating is inhibited by the injection of 0.1 cc. of 2 per cent novocaine; no sweating is observed when the opposite arm is immersed in hot water. In a patient in whom cutaneous nerves had been sectioned, sweating could be obtained by stimulation until the fifth day after operation. In a

patient who had sustained a unilateral sympathectomy, no sweating was observed after stimulation of the sympathectomized arm. Sweating could not be produced in atropinized subjects, which Bickford explains on the evidence of Dale & Feldberg, that the sweat nerves are cholinergic in function. In the same subject, the goose skin produced by faradism was unaffected. Bickford's results are of interest, but some of his conclusions seem rather sweeping for the volume of evidence submitted.

Lisi & Peet studied sweating responses after the subcutaneous injection of pilocarpine and mecholyl and proved that these drugs act peripherally. They considered the evidence that two sets of cholinergic fibers are present, a postganglionic sympathetic and a parasympathetic. Guttmann studied the sweating of a skin graft, transferred from the chest to a portion of the palm. The regional sensory changes are recorded, and the sweating of the grafted skin found to correspond to the region from which it was taken. The mechanism of reestablishment of sweat function in grafted skin is discussed, but unfortunately, no observations had been made on the patient until one and a half years after operation.

The protective effect of sweat on the skin against ultraviolet irradiation has been studied by Crew & Whittle. A film of sweat 0.2 mm. in thickness has a just observable screening effect which is due to dissolved and suspended substances, ether-soluble fatty substances probably playing some role. The average thickness of the sweat on the forehead of a profusely perspiring person was found to be 0.07 mm. Under this condition, possibly seventy-five per cent of the solar irradiation would be effective, and under conditions of prolonged sweating, the protection against sunburn is probably greater.

Further various studies of the contents of sweat have become available. Wright & MacLenathen have found the concentration of ascorbic acid to range from 0.024 to 0.86 mg. per cent in patients during heat therapy. The intravenous injection of vitamin C did not increase these values significantly, and the urinary excretion was low.

Cornbleet reports determinations of the bromine content of sweat and of exfoliated epidermal cells. The subject is of clinical interest because of marked skin changes which may follow the ingestion of bromide. In normal persons, Cornbleet found un-

filtered sweat to contain from 18.2 to 50.2 μg. of bromine per 100 cc. and filtered sweat from the same subject, 16.5 to 41.2 μg. Following ingestion of three grams of sodium bromide per day for one week, these values increased to 45.6 to 152 and 35.2 to 63.4 μg., respectively. The sweat glands and kidneys both have only a limited capacity for the excretion of bromides. The content of bromine in the epithelium may increase enormously, and even in patients with exfoliative dermatitis receiving no bromine, considerable quantities are present. This study is of significance in explaining, to some degree, the slow involution of bromine eruptions, even in persons under treatment with large amounts of chloride.

The lactic acid content of sweat has been further studied by Radsma & Nizar in four subjects working on a bicycle ergometer. Five to twenty times as much lactic acid was excreted in the sweat as in the urine, and an increase in the temperature of the room from 23° to 28° resulted in a two- to three-fold increase in the sweat lactic acid, and only a slight increase in the urine lactic acid. It is suggested that some of the lactic acid in the sweat is a product of the skin itself, but this seems uncertain on the basis of the evidence submitted.

Keutmann *et al.* record electrolyte balance studies done on human patients during fever therapy. The skin losses of sodium and chloride represented seven per cent to nineteen per cent and the net losses seven per cent to twenty-two per cent of the amount estimated to be in the extracellular water at the beginning of treatment, the differences being due largely to variations in the sweating ability. The importance of adequate available stores of sodium chloride before treatment and replacement of water and sodium chloride during treatment is again emphasized.

Various constituents of the skin.—The levels of a variety of inorganic and organic substances of the skin have been determined, though their significance is not always clear. Sellei & Spiera have published further data on the skin of white rats as a storage organ for carbohydrates. Carandante studied the distribution of potassium in the human skin by histologic methods, and found the epidermis to be particularly rich in this element. Alquier & Michaux found the ratio of calcium to phosphorus of the rabbit skin to be 0.11 at birth and to increase steadily until it is 0.51 at sixty-five

days. The blood ratio decreases from 0.34 at birth until it reaches a constant value of 0.1 to 0.18 after thirty days. Eggleton records the zinc content of epidermal structures, varying in man from 255 parts per million of fat-free dry matter in the head hair to 26 parts per million in the skin. Pigmented and non-pigmented skin showed similar values. The cast-off skin of snakes contains large amounts of zinc. Eggleton concludes that the zinc content of epidermal tissues is largely a reflection of the feeding habits of the animal.

Steinbrück has further studied the well known storage of arsenic in human hair and other tissues and emphasizes the wide variations in the amount of this element.

Lipid physiology.—The study of the lipids of the skin is exciting increasing interest, entirely aside from the large volume of clinical reports concerned with the skin in general lipoid diseases. Various considerations have excited this interest: the possible relation of cholesterol to various hormones; the fat-soluble vitamins in the skin; the probable great importance of cholesterol and its esters in the protective functions of the skin; the possible significance of varying proportions of lipins in the physiology of the skin; and the possible relation of lipids to skin tumors. Knudson *et al.*, in an extremely interesting paper, have recorded the cholsterol content of the skin, blood, and tumor tissue in rats irradiated with ultraviolet light according to the technique of Beard *et al.* During exposures of twenty hours daily, skin lesions began to appear after two months, and tumors on the eyes, ears, and the nose after five months. The total cholesterol content of the skin, particularly on the face, increased greatly, practically all the increase being in the ester form. On the back and abdomen the rise was only slight. The increase in total cholesterol was not related to the period of irradiation. The cholesterol in the skin tumors was high and, in contrast to the proportion of free cholesterol of 33 per cent in the skin of the face, was about 80 per cent. Surprisingly enough, the total cholesterol of the blood in the rat with tumors was below the normal level. In rabbits Villela has noted an increase in the skin cholesterol during experimental hypercholesterolemia.

In a recent paper, Koppenhoefer records the continuance of his interesting studies of the various lipin fractions of the several skin layers. Partridge finds the epidermal lipids to contain a large

proportion of highly unsaturated hydrocarbons and of total cholesterol, while the corium lipids are predominantly triglycerides. Muscular exercise is accompanied by an increase in the phospholipins, a tendency for the lipids to become more saturated, and the loss of triglycerides in the epidermal fractions.

Engel finds that after irradiation of rabbits for three to six weeks with ultraviolet light, a substance appears in the blood and skin which causes vaginal cornification in castrated female mice. The formation of this substance is not influenced by the injection of cholesterol, nor does irradiated or non-irradiated cholesterol produce estrus in the castrated rat or mouse.

The changes of the skin in relation to general and local lipid disturbances have been summarized by Montgomery & Osterberg, among others. Blank finds that saturated fatty acids of low molecular weight yield a much higher percentage of positive reactions to patch tests than do acids of higher molecular weight.

Keratinous substances of skin.—Block, continuing his studies of the chemistry of keratin, determined the nitrogen, sulphur, and various amino-acids in fourteen eukeratins and found that the proportions of histidine, lysine, and arginine were relatively constant. Marked variations were noted in the content of cystine, tyrosine, tryptophan, phenylalanine, and glycine. On the other hand, Pillemer & Ecker found the cystine content of keratins prepared from human hair, wool, and chicken feathers to be essentially the same, as was the nitrogen and sulphur content and isoelectric point. These investigators also report a species specificity of serological reaction with these keratins, and a specificity dependent on oxidation or reduction at the sulphur linkage.

Some other physiologic studies of hair and feathers are available. Volker found porphyrin to be present in the feathers of three natural orders on the basis of fluorescence produced by illumination with ultraviolet light. The amounts were small, except in bustards and owls. An ester of coproporphyrin III was obtained from some feathers.

The high flavin content of eel skin with histological localization of the pigment in melanophores has been confirmed in other non-scaly fish by Fontaine & Busnel. In scaly fish, such as the carp, a substance which is not flavin but is closely allied, insoluble in chloroform, and showing a blue fluorescence, has been found in association with the melanophores.

A method for determining the firmness of human hair roots has been devised by Bastan, and the load required for depilation determined in various regions of the body. During its growth the "firmness" of the average hair increases from 15.4 gm. to 31.8 gm. and then decreases somewhat. In red human hair Arnow (18) has been able to express a red-brown pigment by prolonged boiling of the hair with 0.1 N HCl. The absorption spectrum and other properties of this agreed with the substance produced by mild oxidation of melanin from "dopa" in an alkaline solution. This would appear to be further evidence of the identity of "dopa" and the precursor of physiologically produced melanin.

The effects of radiation on the skin.—Recent reviews of the effects of ultraviolet irradiation on the skin are available in the papers of Laurens and of Mitchell. The latter believes that the erythema produced by ultraviolet light is related to a photochemical decomposition of the proteins in the stratum mucosum, the product possibly being a proteose. The latent period is explained, in part, by the time required for a diffusion of the decomposition products to the blood vessels. Mitchell sets the wave length of maximum erythema production at about 2975 Ångstrom units.

Hetzar points out that determinations of x-ray sensitivity by the production of erythema or epilation may not be reliable and used a large dose (1950*r*) at 70 kv. on an area 4 cm. square in rats. In one month a characteristic reaction was obtained, with ulceration, and peeling. Castration or the menopause was associated with increased tolerance in females. Ingestion of thyroxin produced an earlier and more intense x-ray reaction, the reverse being true in thyroidectomized rats.

Shaffer has studied the effect of x-rays in humans on skin reactivity to histamine and bacterial vaccines. His results in the effects on histamine wheals seem definite. The wheal produced by injection one hour after a single exposure of 125*r* of low-voltage unfiltered x-rays, tended to be larger on irradiated skin, while if the injection were made two to five days after treatment, the wheal was smaller. The size and intensity of the erythematous flare was less in both instances.

Miscellaneous topics.—Various studies of electrical phenomena in the skin are available, though their significance is often not clear. Barnett has described an improved technic for measurement

of the phase angle of the skin. In 120 normal subjects, the angle was found to vary between 64° and 78°, at 15,300 cycles. Barnes has studied the influence of heavy water and the temperature on the electromotive force of frog skin and notes that cooling causes a fall, and that on the re-warming of the skin, the electromotive force rises beyond its original value. Ninety-five per cent deuterium oxide produced a partially reversible fall of 64.8 per cent.

Various isolated studies of other skin functions have become available. Burtenshaw describes a technic for recovering microorganisms from the skin. A definite variation in the disinfectant power of the normal skin surface was noted, being greatest in the regions of greater acidity. The disinfectant power of rubber is also considered. A method for the determination of skin distensibility has been devised by Sodeman & Burch, consisting of spring calipers attached to the skin by collodion and bakelite tubes, placed 5 cm. apart with an exerted force of 100 grams. The comparative distensibility of various areas of the body, and of the skin in scleroderma, atrophy and edema was determined. In scleroderma there was a marked diminution, and also in heart disease as the edema increased.

Dun & Finley have published an interesting study of the rate of adaptation of cutaneous nerve endings in the frog. It was found that the discharge produced in sensory nerve fibres by stretching of the skin was similar to that produced by moderate and strong pressure, apparently indicating that the brevity of discharge could not be due to a purely mechanical adaptation of the tissues to the stimulus, but expressed some genuine constitutional property of the nerve endings. The duration of this discharge could be increased by reduction of calcium, and long duration could be reduced by an excess.

Silverman has described a chemiotactic power in pulped normal human skin, examined by the McCutcheon technic. The power was lost if the skin were extracted with water. The positive chemiotaxis of agar and negative chemiotaxis of kaolin were found to be unaffected by changes in the hydrogen ion or salt concentration, suggesting that the simple physicochemical factors are not important.

Changes in the growth of mouse skin produced by cysteine disulfoxide, dibenzanthracene, and thiocresol applied in ointment

form have been studied by Reiman. Examination of the skin in microscopic preparations showed that these substances produced after three weeks of daily application, a growth of 1.2, 1.5, and 3 respectively, as compared with a normal value of one. In the skins treated with dibenzanthracene, there was disorientation.

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ENERGY METABOLISM

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Professor Murlin, in his excellent chapter on energy metabolism in the first volume of the *Annual Review of Physiology*, not only covered the literature from July, 1937, to October, 1938, but also in several important instances correlated the papers appearing that year with the older literature on which they were based. The present review includes only the literature from October, 1938, to October, 1939, and is brief because fewer important papers have appeared during this period than in the former; the material is too diversified to attempt a correlation of the reports of this past year with earlier studies. Also the papers referred to do not represent a complete bibliography.

Basal metabolism of human beings.—The various respiratory functions of a series of fifty normal boys and fifty normal girls, representatively sampled from normal school children, were studied by Shock & Soley. Tests were begun at the ages of eleven or twelve years and were repeated at intervals of six months over a period of five years. An additional group of forty-six normal adult males and forty normal adult females, ranging from twenty-seven to forty-three years of age, were also studied. Determinations of basal heat production were made by the open circuit or gasometer method, the analyses being made with a Haldane gas analysis apparatus; three eight-minute tests were run after a ten-minute rest period on each of two successive days. The subjects were brought by automobile from their homes at 7:30 each morning without breakfast. The results are summarized in table 1.

TABLE 1

Heat Production of Normal Subjects in the Different Age Groups
(*in kilocal. per sq. m. per hr.*)

Age in years	11.75–12.24	13.75–14.24	15.75–16.24	18.00–26.99	27.00–43.00
Male	45.03	43.46	41.13	36.57	35.44
Female	40.99	37.96	34.29	34.28	32.63

A study of the basal metabolism of 110 college women and fifty college men between the ages of seventeen and twenty-seven years has been reported by Rogers. The data are presented for the men and women in distribution curves of the percentage variation (together with the mean variation) from the standards published by (1) Boothby, Berkson & Dunn, (2) Harris & Benedict, and (3) Aub & DuBois and are summarized in table 2.

TABLE 2

DEVIATION OF BASAL METABOLISM OF COLLEGE STUDENTS FROM ACCEPTED STANDARDS
(*in per cent of normal*)

STANDARD	WOMEN			MEN		
	Mean	High between	Low between	Mean	High between	Low between
Boothby, Berkson & Dunn	−0.4	+15 +20	−15 −20	−2.5	+15 +20	−15 −20
Harris & Benedict	−1.9	+20 +25	−10 −15	+0.8	+20 +25	−10 −15
Aub & DuBois	−2.3	+15 +20	−15 −20	+1.6	+15 +20	−15 −20

Talbot, in a study of the basal metabolism of undernourished girls, found that in both acute and severe chronic states of undernutrition there is a decrease in the rate of heat production. However, he pointed out that although the absolute heat production is diminished, it may appear to be increased if there is a greater proportional loss in inert tissues than in heat production. He believed therefore that any of the generally accepted standards based on observed body weight, including surface area calculated from body weight, as well as the "multiple prediction formula" may give an erroneous estimate. Therefore, he recommended that the absolute total heat production be compared with standards expressed in terms of expected average weight for height.

The relationship between total calories and excretion of creatinine is approximately as accurate as that between total calories and either height or weight. Therefore, the number of milligrams of creatinine excreted in a twenty-four hour period may be used

for the prediction of normal heat production for children in the same manner that height and weight have been used in the past. These were the conclusions of Talbot, Stewart & Broughton.

In an attempt to improve the basis of comparison of heat production of children with abnormal bodily dimensions, de Bruin studied first 120 normal boys and 123 normal girls whose body weights ranged from 6 to 46 kg. On the basis of the figures thus obtained, standard curves of heat production for normal children were drawn up on the basis of weight. He then determined the metabolism of 107 children with abnormal bodily dimensions and recommended an arbitrary increase in the standard for boys who are more than 35 per cent overweight and for girls who are more than 20 per cent overweight, the rate being based on the standard weight (for the actual height) increased by one-third of the excess over the standard weight. Change in the standard was not thought necessary for thin boys and girls or for well proportioned children who were too large or too small for their age.

Tepper & Hellebrandt found an average increase in seventy-five women on standing passively of 5.71 kilocal. per sq.m. per hr., 16.3 per cent greater than that found in recumbency. The increase on standing varied markedly from subject to subject, and a relation was postulated between the energy cost of standing and the type of contraction necessary for maintenance of the stance.

The basal metabolism of young healthy Indians was studied by Ahmad, Lal & Roy under two sets of atmospheric conditions: (1) in the ordinary warm and humid conditions during the monsoon season in Calcutta, where the temperature was between 85° and 90° F. (29.4° and 32.2° C.) and the relative humidity between 67 and 80 per cent, and (2) in an air conditioned room where the temperature was between 75° and 80° F. (23.9° and 26.6° C.) and the relative humidity between 51 and 59 per cent. Nine subjects were studied and observations were made twice under each condition. The rate of heat production unmistakably decreased in all of the nine subjects on going into the air conditioned room; the amount of the decrease varied between 5 and 10 per cent. It should be emphasized that these results were obtained on the basis of a sudden change in atmospheric conditions. The basal metabolism of all subjects was slightly lower than the standards of DuBois, Harris & Benedict, and Dreyer; in the air conditioned room it was decreased 16.8, 12.1, and 12.4 per cent, respectively.

Rajagopal found the basal metabolism of twenty-six native Indian men to be eight per cent less than that of twenty European men living in identical climatic conditions in Coonoor, at an altitude of 6,000 feet. He also observed that the basal metabolism of seventeen Indians who had lived in this cool and dry climate of the hills for more than three years was significantly higher than that of the nine Indians who had gone up there more recently.

The average basal metabolic rate for six male and seven female Chippewa Indians living in northeastern Canada, as reported by Crile & Quiring (1), was found to be 18.0 per cent and 18.5 per cent respectively above the Mayo Foundation Standards. Thirty male Eskimos averaged 16.4 per cent and thirty-three female Eskimos averaged 29.0 per cent above that standard, although if the values above +40 per cent were excluded, their average values fell to +14.5 per cent and +21.1 per cent, respectively. On the other hand, they found [Crile & Quiring (2)] a smaller increase, averaging +8.2 per cent, in thirty Maya Quiché Indian soldiers stationed at an altitude of about 8,000 feet in Guatemala, Central America.

Metabolism and temperature regulation.—The heat production of the fasting rat in relationship to environmental temperature has been investigated by Swift & Forbes who found, in a series of 122 eight-hour periods of measurement, that (1) the critical temperature for the fasting rat was 30° C., (2) the metabolism remained constant over a range of temperatures extending from 30° C. to 33° C., and (3) the percentage of total heat eliminated as latent heat of water vapor increased steadily from 7.9 per cent to 59.2 per cent with a rise in environmental temperature from 7.5° C. to 35° C., although the absolute amount of heat eliminated in this manner was practically constant up to 31° C., above which a definite increase took place.

The role of the thyroid gland in the mechanism of elevation of the metabolism due to exposure to cold was investigated by Ring who found that rats who lived for three weeks at a temperature of 0 to 5° C. had an average elevation in metabolism of 21 per cent (corrected for changes in body temperature, this figure becomes 16 per cent) if the thyroid gland is intact, whereas only a slight increase occurred in thyroidectomized rats; nervous pathways through the superior central ganglia were not essential for bringing about stimulation of the thyroid gland by cold.

Carbohydrate and fat metabolism.—Talbott, Coombs, Consolazio & Pecora studied the effect of large amounts of sucrose, glucose, and levulose on five subjects. Five adult males, asthenic in appearance, were observed for two to seven weeks on a diet adequate with respect to protein, fat, minerals, and vitamins and fortified by the daily addition of from 430 to 700 gm. of sucrose, glucose, or levulose. The respiratory quotient and oxygen consumption were determined approximately every third day during the respective periods of observation; a six hundred liter gasometer was used for collecting expired air by the open system. Each determination was begun approximately sixteen hours after the evening meal of the previous day and twelve hours after the last ingestion of sugar solution. It was continued for fifty minutes in order to minimize transient variations in the respiratory quotient which may be observed in ten-minute periods of collection. According to the findings of these authors, there was a rise above unity of the postabsorptive respiratory quotients following ingestion of each of the three sugars. The maximal elevation was observed in the two experiments in which sucrose was employed. In one, the respiratory quotient was 1.21 on the fifth day and decreased to 1.09 on the ninth day. In the other, the respiratory quotient reached 1.22 on the sixth day, remained above unity until the twentieth day, and decreased only to 0.9 on the forty-fifth day of the experiment. In the two subjects who received glucose as the added sugar, the respiratory quotients, which were quantitatively similar, reached or exceeded 1.05 by the ninth day and remained above unity during an elapsed time of approximately three weeks, and then reached the same order of magnitude as in the experiment with sucrose. In the experiment with levulose, the respiratory quotient was 1.05 on the eighth day but decreased to 0.96 two days later and remained below that observed for the other sugars throughout the remainder of the period of observation.

The metabolism of two subjects, who were not in athletic training, before and after a walk of ten miles in the postabsorptive state, was investigated by Mills. One subject who lived habitually on a high carbohydrate diet showed an inconstant lowering of the respiratory quotient after the walk but there was neither ketonuria nor depression of the glucose tolerance even when the carbohydrate in his diet temporarily was restricted. The other subject, who

habitually consumed a lower proportion of carbohydrate, always showed a low respiratory quotient and ketosis after the walk, unless he greatly increased the carbohydrate in his diet; his glucose tolerance was considerably lowered after the walk, but if he had been living on a high carbohydrate diet, this depression would have been absent; insulin was found to raise the respiratory quotient much farther after exercise than before.

Effect of various factors on metabolism.—Kleiber found that baby chicks from five to twenty days of age showed an increase in metabolic rate with increasing age. This increase was 0.2 to 1 per cent per day per unit of body weight, 2 per cent per day per unit based on the three-quarter power of the weight, and 3 per cent per unit of surface area.

As reported by Barbour, Porter & Seelye, chronic morphinism elevated the average resting metabolism of dogs for the entire twenty-four hours to ten per cent above normal in the second to fifth months of chronic morphinism; the peak of the stimulation after the daily injection appeared sooner, as tolerance to the quieting effect of morphine developed. The authors concluded that morphine exerts marked influence as a metabolic stimulant independently of neuromuscular activity.

Wilbrandt, Wilbrandt & Steinmann demonstrated that acute anoxemia increased the oxygen consumption by about 21 per cent, the subjects being in a chamber with pressure corresponding to an elevation of 6,000 to 7,000 meters; during ascent, carbon dioxide was washed out (of the blood with a rise in respiratory quotient) and during descent, there was a gradual reaccumulation of carbon dioxide (as shown by a fall in respiratory quotient).

Sylla reported that patients who have congenital anomalies of the right side of the heart usually have a lowered basal metabolic rate.

The intravenous injection of calcium chloride, sufficient to increase the serum calcium from 10.5 to 11.5 mg., was reported by Goreczky & Ludány to decrease the oxygen consumption about ten per cent in ten minutes.

The effect of vitamins on the respiratory metabolism varies considerably, according to Göthlin. Vitamins B_1 and D have a marked effect in increasing rate of oxidation, whereas vitamins A and C have no demonstrable effect.

Rupp found no effect on the metabolism of rats from the ad-

ministration of an ovarian hormone. Hoffmeister reported that castration decreases the basal metabolic rate by about ten per cent, which is accompanied by a slight increase in weight due to accumulation of fat.

No definite antagonism between the sympathetic nervous system and the parasympathetic nervous system with regards to the oxidation processes was found by Mertens & Rein.

Inercitrin injected intraperitoneally in doses of 12 mg. per kilogram lowers the metabolism of normal rats about 8 per cent; simultaneous injection of inercitrin decreased by about one-half the increase in metabolism produced by dinitrophenol alone, according to a report by von Jeney & Vályi-Nagy.

According to Berggren & Söderberg, in experiments on two healthy men, 20 mg. of amphetamine administered orally causes a a rise of about ten per cent in basal metabolic rate and an increase of cardiac output; the latter was proportionately greater, as was shown by a fall in the arteriovenous oxygen difference.

Carpenter & Lee (1), in an extensive article, have shown by excellent technic that (*a*) the metabolism of alcohol, as indicated by the course of the respiratory quotient and the oxygen absorption, proceeded at about the same rate irrespective of whether the subject was at rest or engaged in muscular activity; (*b*) the efficiency of performance of work was not significantly altered; (*c*) muscular work does not increase the rate of combustion of alcohol; and (*d*) they found no indication of a summation of the separate effects of ingestion of alcohol and muscular work when the effect of both these factors was simultaneously brought to bear on the basal metabolism. The same authors (2) showed also that muscular work did not appreciably alter the concentration of alcohol in urine, in blood, or in expired air (as shown by measurements of amounts eliminated per liter of expired air); the alcohol eliminated per liter of carbon dioxide was unchanged. The amount of alcohol eliminated by respiration was about twice as much during work as during rest, but as this only amounted to 0.4 to 0.7 per cent of the amount ingested at rest, and from 0.9 to 1.6 per cent of the amount ingested in the work experiments, this played a negligible role in reducing the amount of alcohol in the body.

A report by Hindemith indicates that subcutaneous doses of 100 mg. of caffeine per kilogram increases the consumption of oxygen in the first two-hour period by 28 per cent. The maximal effect

came in the second two-hour period, with a 35 per cent increase followed by a gradual decrease to the period between twenty-six and twenty-eight hours after ingestion when it had decreased to about +19 to +15 per cent; after a further period of twenty-four hours, it was still increased above normal by 5 per cent. The effect of 50 mg. of caffeine per kilogram was very much less, with a maximum of +15 per cent followed by return to normal at the end of six hours; no effect was obtained from 25 mg. of caffeine per kilogram.

Hering reported that the specific dynamic action in rats produced by *Brenztraubensäure* (29 per cent pyroracemic acid) is greater than that produced by alanine (14 per cent) and he concluded, therefore, that the diaminized nitrogen-free remainder plays a role in the specific dynamic action of amino acids.

Kriss found that there was greater absorption of some amino acids when added as a supplement to a mixed maintenance diet of rabbits; also, the amounts excreted in the urine varied. Proteins were more completely metabolized than were the single amino acids. A correlation was found to exist between the respiration and energy factors, and the ratios of carbon to nitrogen in different amino acids and proteins. Kriss suggested that when more experimental data become available it will probably be possible to derive a general formula, for practical use in indirect calorimetry, for the calculation of respiration and energy factors for any protein, and possibly for any amino acid.

Hormonal effects.—Mahaux found that (1) the injection of 9 mg. of thyroxin into rabbits not only inhibited but inverted the action of the thyrotropic hormone subsequently injected (exophthalmos developed despite this); (2) the injection of 3 mg. of thyroxin was not sufficient to impede the hypermetabolic action of the subsequent injection of thyrotropic hormone (exophthalmos was accentuated); (3) the simultaneous injection of 3 mg. of thyroxin plus thyrotropic hormone brought about an inversion of the immediate action of this extract, with a fall in metabolism to less than normal (accompanied by a severe degree of exophthalmos). The fact that 3 mg. of thyroxin plus thyrotropic hormone, simultaneously injected, is followed by an inverse action of the thyrotropic hormone analogous to that produced by 9 mg. of thyroxin was interpreted by Mahaux as indicating that the thyrotropic hormone sensitizes the nerve centers to thyroxin.

Meyer & Wertz reported a few experiments which indicate that the percentage metabolic increase, plotted as a function of dosage of thyroxin, follows a logarithmic curve; they also found that between 0.19 and 0.25 gamma of thyroxin, given as thyroid globulin, was three to four times more potent than the racemic substance.

Friedgood & Bevin stimulated faradically the cervical sympathetic nerves of twenty-two rabbits for periods of one-half to four hours; in twelve of these, there was no significant change in basal rate of oxygen consumption; in eight rabbits, there was some irregular increase in consumption of oxygen, but it was not maintained for more than a few days; in two rabbits, there was a marked increase which persisted for several days although at necropsy, in one instance, the gland exhibited no characteristic histologic signs of hypersecretion. The authors concluded, therefore, that the secretion of thyroglobulin is not accelerated by excitation of the cervical sympathetic nerves alone.

Cammer & Griffith found that epinephrine injected intra-arterially in any effective concentration reduces blood flow and oxygen consumption in the hind leg of the cat; the output of carbon dioxide is affected in a more complex manner, suggesting a nonoxidative effect and removal dependent on the rate of effective blood flow. They interpreted their results as indicating that the calorigenic effect of epinephrine is exerted elsewhere than in the peripheral tissues.

Kleiber & Cole found that daily injections over a period of six months of alkaline extract of anterior pituitary glands of beef (Evans' growth hormone preparation) into twenty-two female rats, stimulated growth. The thyroid glands of the injected rats were relatively smaller and their adrenal glands absolutely smaller than the corresponding glands of the controls. The fasting catabolism of the rats was measured in respiratory trials of four hours' duration during the period of injections, as well as after cessation of the injections (127 trials on injected rats and 118 on controls). The metabolic rate of the injected rats per unit weight and even per unit surface was consistently and significantly lower than the corresponding rate of the controls. This result was observed during the period of injection, as well as after cessation of the injections. These differences in the metabolic rates per unit weight of giant rats and normal litter mates evidently cannot be explained by genetic differences. Neither can they be explained by changes in

the water or protein content of the rats. The rate of oxygen consumption per unit of dry weight of tissue *in vitro* was smaller in the diaphragms of the injected rats than in the diaphragms of control animals. This difference obviously cannot be related to genetic differences of the tissues; it indicates that the respiration of tissues *in vitro* is still affected by the previous condition of the animal. The authors regarded their results as an example of somatic adaptation of tissue metabolism *in vivo* as well as *in vitro* to a condition of the animal as a whole, particularly to its endocrine system, which is in correlation with body size.

During the past year, there has been a continuation, in Collip's laboratory at McGill University, of studies on the activity of the specific metabolic principle. The more important phases of this are presented in the article by O'Donovan & Collip. After reviewing the literature, the authors presented evidence to show that there are two metabolic stimulants in pituitary extracts: one, the thyrotropic hormone which stimulates metabolism by activating the thyroid gland; and another, which acts independently of the thyroid gland and has an immediate but transitory effect lasting a few hours after injection. Evidence that this immediate effect is distinct from the thyrotropic hormone was garnered from the fact that an increase in consumption of oxygen resulted in thyroidectomized rabbits. Further evidence that the immediate rise is due to a factor other than the thyrotropic hormone is obtained from the relative resistance of the two substances to high temperature. The pituitary extract boiled for one hour at approximately pH 7 contained no appreciable amount of thyrotropic hormone, as indicated by its failure to produce hypertrophy of the thyroid gland of treated guinea pigs, while it was still active, in so far as the immediate rise in metabolism was concerned, even after boiling for two and a half hours. Additional points of distinction between the thermostable metabolic and thyrotropic hormones were based on the development of resistance to the thyrotropic effect without a corresponding resistance to the immediate metabolic effect, the longer latent period of the thyrotropic hormone, and, finally lack of parallelism between the two activities in various extracts. The most potent metabolic preparations were low in growth promoting adrenotropic, and prolactin activity. The latter, as well as oxytocin and vasopressin, may be definitely excluded by the susceptibility to alkali and high temperatures observed. The close similarity of

the metabolic stimulant to the melanophore dilating hormone is evident from a similar distribution in the various parts of the pituitary gland, from a common resistance to the action of alkali at the temperatures of the boiling-water bath, and from absorption by charcoal and digestion by trypsin. In addition to its effect on the consumption of oxygen by rabbits, the specific metabolic stimulant of O'Donovan & Collip depresses the respiratory quotient. The production of carbon dioxide is increased, especially in fasted animals, and the body temperature rises. There is evidence of decreased nitrogen metabolism. The hypothesis that fat metabolism is stimulated is advanced; but the depression of the respiratory quotient being large in comparison to the increase in oxygen consumption, it appears that there must be, in addition, some suppression of carbohydrate oxidation or some increase of gluconeogenesis. Extracts have been prepared from pituitary glands of oxen, sheep and pigs; the active principle is present in both anterior and posterior lobes but has been found in highest concentration in pituitary colloid and in extracts of the pars intermedia.

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HEART[1]

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Anatomy and Embryology

Very little of physiological moment has appeared regarding the anatomy of the heart. Robb (1), continuing her work on the distribution of Purkinje fibers, reported a plentiful supply in the anterior portion of the septum, permitting transmission of the impulse here without delay. Patek (2) studied the distribution of the lymphatics and found three extensive networks, a subendocardial, a myocardial, and a subepicardial, consisting of vessels larger than blood capillaries and showing drainage from the inside toward the outside of the heart. Harper (3) confirmed the finding that injury, in this case mechanical, might lead to vascularization of a heart valve.

Several important contributions pertaining to the physiology of the embryonic and neonatal heart have appeared. Closure of the foramen ovale in the lamb was found to occur after closure of the ductus arteriosus (4). The latter occurred anywhere from 30 sec. to 6½ min. after delivery, sometimes before the umbilical cord was tied off or air was visible in the trachea (4, 5); the former occurred eight hours after birth (4). The authors employed an ingenious method using x-ray cinematography and the injection of radiopaque material.

The atrium in *Amblystoma punctatum* contracts several hours before the circulation starts; two to three days later the sinus venosus becomes the pacemaker (6). The inherent rate was shown to decrease from the sinus to the bulbus cordis and truncus arteriosus. The first contraction in the 9½ day old rat embryo, suspended in a hanging drop culture, occurs in the left ventricle near the atrioventricular constriction; two hours later the right ventricle begins to contract. The two contractions are independent until

[1] This review covers the period from June, 1938, to August, 1939, although a few earlier references are included in the section on coronary flow. The limits of space prevent an adequate discussion of more than a few of the more important contributions.

they extend and meet in the midline, when the left, the more rapid, dominates (7), At this time no contractions are evident in the venous side of the heart and the circulation does not appear until twelve hours later.

In the chick embryo the relation between the pattern of contraction and the electrocardiogram (axial lead) was studied by Patten and his collaborators (8). They showed that a diphasic electrical undulation, 0.5 sec. in duration, is present at the 33 to 36 hour stage; at this time the ventricle is stimulated erratically and its impulse travels slowly. At 37 to 40 hours, an inverted QRS complex, a depressed S-T segment, and a small upright T wave are seen; at this time the ventricle is stimulated from a point near its upper end, and its impulse travels rapidly. Two or three hours later, as the atrial region develops, a P wave with a T_a wave is seen 0.08 sec. ahead of the QRS complex. In the four day old chick the electrocardiographic deflections have taken on the configuration seen in post-natal life. These changes appear before there is any histologically demonstrable evidence of the specialized conduction tissue.

Cardiac nerves do not appear to operate until some days after birth; the vagus first becomes active on the eleventh to the eighteenth day in the puppy and rabbit (9, 10, 11), and the sympathetic, by the second or third month (9). The carotid sinus appears to function in response to axphyxia as far as the heart is concerned after the fortieth day (12).

Automaticity, Conductivity, Irritability, and the Refractory Phase

The superior vena cava of the guinea pig shows a syncytial structure which undergoes rhythmic activity (13). All parts of the surviving sinus venosus and large vein of the turtle show rhythmicity and contractions (14). Studies have been reported concerning the behavior of surviving Purkinje fibers in the dog and beef heart (15, 16).

Puddu & Cammarella (17) were able to demonstrate in a case of complete ectopia cordis pectoralis that the impulse originated in the region of the sinus node and spread uniformly through the atria. All parts of the ventricles were stimulated in quick succession, with the apex a trifle ahead of the base.

Potassium was shown to double the chronaxie of the isolated perfused heart and removal of potassium to decrease it; calcium was without clear effect (18). Large changes in sodium chloride altered chronaxie by an osmotic action (18). Potassium increased electrical conductivity of the heart (18). Outside of an osmotic effect, changes in sodium, potassium, and calcium had no influence on the frog's heart rate (19). Gilson (20) reported that increasing the ratio of calcium to potassium or decreasing the sodium bicarbonate concentration resulted in a period of supernormality of response in the excised turtle heart, followed by a period of subnormality. Segers (21) found that a polarization current altered the rate of the isolated frog's heart, the new level being attained only after a lag; the reverse occurred when the current was discontinued. This has been confirmed in the turtle (22). This accommodation to the polarizing current depends on the ratio of calcium to potassium (23). When the polarization current (in the toad, tortoise, and frog) was such that the interior of the heart was negative with respect to the outside, the heart rate increased, and vice versa (24). In the eel, a polarizing current applied to the heart with the negative pole at the sinus node resulted in an increase in the heart rate; the reverse occurred when the positive pole was at the sinus node (25). Similar changes in heart rate occurred in the isolated frog heart when the perfusion pressure was altered; an increase causing acceleration, a decrease deceleration (26). A delay in attaining the new rate level occurred here also.

The rate of the cardiac pacemaker is related to its oxygen consumption (27, 28). In the toad's heart after a period of forced acceleration, slowing and sometimes temporary cardiac arrest developed (29). Reports have appeared concerning the action on the rhythmicity of the sinus node in response to certain physical procedures (30); to asphyxia, carbon dioxide, and anoxemia (31, 32, 33); to anesthetics (34, 35, 36); to sympatheticomimetic amines (37, 38, 39, 40, 41, 42); and to other drugs (43, 44, 45).

Reflex changes in heart rate follow irritation of the nasal mucosa (46, 47). On a statistical basis, the heart rate in normal males is reported slowest between the ages of twenty to twenty-five years; however, the correlation is not very close (48). The pulse rate of man was again shown to be higher in the tropics than in

cooler climates (49). Tilting of the body with the resulting pooling in and emptying of blood from the lower extremities caused heart rate changes—the heart rate increasing when blood was returned to the heart from the legs (50); these changes seem to be proportional to the amount of blood pooled. Changing from a reclining to a sitting posture accelerated the pulse rate (51). The reflex nature of the acceleration of pulse rate occurring in a limb rendered ischemic is confirmed by the absence of such acceleration upon inducing ischemia in a limb deprived of sensory innervation (52).

Dogs kept on a diet of Purina and cod-liver oil for four to five weeks developed a bradycardia which was not abolished by atropine (53). Thiamine and yeast did not reverse this slowing but uncooked chow did so within twenty-four hours (53).

The fastest pacemaker (the sinus) gains control when the toad's heart is split so that a U is formed with the sinus at one end and the bulbus at the other (54).

The isolated left atrium of the rabbit and guinea pig showed an occasional contraction (55), and this was made more rhythmic by the "active substance" of Demoor (56). This latter material also resulted in a sensitization of the preparation to epinephrine and acetylcholine (56).

In the frog's ventricle acetylcholine and acetyl-β-methylcholine shortened the refractory period (57, 58). The effect was abolished or prevented by atropine (58). Potassium is reported to be without effect in these studies (57), although others find that it lengthens both the absolute and relative refractory phase (61). Epinephrine, ephedrine (59) and the dioxane derivative, 933F (60), prolong the refractory period. Cooling lengthens the entire refractory phase, while the addition of acids lengthens only the relative refractory phase (61). Under various influences the changes in refractory phase duration are not parallel to the changes in duration of the monophasic action current (61). The absolute refractory phase lasts to the end of the plateau of the monophasic curve; the relative refractory phase terminates at about the end of the monophasic curve (61). Digitalis shortens the refractory phase (264).

A double response may follow a single stimulus of the frog's ventricle (61). During the relative refractory phase there is, therefore, a local residual process which can initiate this repetitive response (61). Evidence is presented to indicate that, in the mammal (62, 63) and in man (64, 65), a supernormal phase may follow

the relative refractory phase when the heart originally is in a subnormal state; this supernormal phase permits the occurrence of a response to stimuli not effective at other times.

The presence of unidirectional block in the atrioventricular junctional tissues which normally prevents impulses from passing from the ventricles to the atria is confirmed in the dog (66, 67). The variations in the ability of this junction to conduct to the ventricles alters independently its retrograde conducting ability as can be shown by inducing extrasystoles at different times in the heart cycle (68).

The ability of freezing (69), of asphyxia (70), of hemorrhage and transfusion (71), of sympathicomimetic amines (72, 73), of magnesium (74), of calcium (75), and of potassium (76) to produce cardiac arrhythmias has been analyzed on a quantitative basis. The interaction of various substances in inducing ventricular fibrillation in man (77) and mammals (78, 79, 80, 81) has been analyzed. DeBoer (82) has found that auricular fibrillation caused by faradic stimulation of one atrium can be stopped by faradically stimulating the other; this is a result, he believes, of the second stimulus abolishing the first. This is used as the basis for a discussion of the circus theory of fibrillation which he favors.

That the position of the heart partly determines the contour of the electrocardiogram of extrasystoles is confirmed on a patient with an exposed heart (83). The view that this can also determine the electrocardiographic records of block within the ventricles, is supported by the work on the asynchronous manifestation of the onset of mechanical activity of the two ventricles in clinical cases with intraventricular block (84).

The ventricular slowing produced by digitalis in auricular fibrillation is in part a vagal action, reversible with atropine, and in part a direct depressant action on the atrioventricular junction tissue, not reversed by atropine (84 a). In the mammal, the sinus bradycardia induced by digitalis occurs even when the vagi are cut; this is attributed to sensitization of the acetylcholine mechanism of the heart by the drug (84 b).

Size, Tone, Distensibility, Contraction, and Cardiodynamics

On applying the Rohrer-Kahlstorf formula to lateral and anteroposterior x-ray silhouettes, the heart volume was found to

be 400 to 900 cc. in males and 300 to 500 cc. in females (85); 6 to 12 cc. per kg. (85) and 7 to 13 cc. per kg. of body weight (86); or 200 to 450 cc. per sq.m. (85) and 250 to 490 cc. per sq.m. of body surface (86), respectively. A new table has been constructed based on 1460 human records, correlating transverse heart diameter in the teleoroentgenogram with body height and weight (87). Considerable promise is given in methods by which the heart chambers and associated structures can be visualized during life by the use of concentrated radio-opaque material (88, 89). During and after exercise the human heart decreased in size (90) but following continued excessive exertion a tonogenic enlargement appeared, which required six weeks to disappear (91). The enlargement was accompanied by a tachycardia (91). Athletes during exertion did not show an increase in the heart size during systole, but only in diastole (92). Raising the arterial pressure in the dog's heart-lung preparation led to an immediate dilatation; in the intact animal a similar pressure rise required one to two minutes to cause such a dilatation (93). In the healthy man no such dilatation is demonstrable following elevation of pressure, but it can be evoked in heart failure (93).

In the surviving rabbit heart, increasing the rate of perfusion into one side of the heart elongated that ventricle and rotated the heart on its long axis; similar elongation of the other ventricle effected rotation in the opposite direction (94). Severe continued exercise resulted in hypertrophy in rat hearts proportional to the degree of exertion; this appeared in six days and involved the right side before the left (95). It required up to 153 days for this hypertrophy to disappear after the exertion was stopped (95). Administration of thyroid extract, as well as thyroxin, resulted in hypertrophy of the heart, mainly of the right side (96).

The thermal stretching response of the frog's ventricle (between 0 and 25° C.) resembles that of the frog's skeletal muscle (97). Its tension-length curve under nearly isotonic and isometric contractions was also similar to that of skeletal muscle (98). That successive fillings of the isolated turtle heart change the curve representing the ratio of diastolic pressure to diastolic volume to a lower level was confirmed (99); this was associated with a decrease in the external work of the heart. Asphyxia had a similar but reversible action (99). Hysteresis was noted when the diastolic pressure-volume curve was compared during filling and emptying of

the ventricle (99). "K-Strophanthosid" had no effect on the diastolic pressure-volume curve of the tortoise (100). Apparently in the lower mammals and in man the increase in contraction resulting from digitalis (101, 102) is not attributable to tone changes (100, 101). The decrease in heart size previously reported in man with the use of digitalis has been confirmed on both normal hearts and those in failure (103). Therapeutic doses did not affect the potassium content of the entire heart. The conclusion was that the mechanism of digitalis action does not involve changes in potassium (104). Anoxia enhanced digitalis action (104 a). However, these phases of digitalis action are still controversial.

A new method of recording the apex beat electrically was described; this can also be utilized for recording the venous pulse (105). During systole the apex of the exposed mammalian heart was found to rotate counter-clockwise (106). In the three-chambered heart there was an equal change in the long and transverse diameters, whereas in the four-chambered heart, most of the apparent motion was in the transverse diameter (107). More careful analysis, however, showed that actually the long diameter change was as great or greater (108). It results from a movement of the floor of the atrium toward the apex (108). This is easily seen in the human roentgenkymograph in hearts with calcified valves. This motion of the atrial floor leads to a systolic acceleration of blood flow toward the heart (109, 110). This is not enough, however, to counteract the systolic arterial emptying of the chest so that during each systole 30 cc. more blood leaves the human chest than enters it (111). Previously the net amount of blood leaving the chest had been underestimated because it was not realized that the chest air capacity actually varies during the heart cycle (111).

The normal roentgenkymographic contour of various points on the edge of the ventricular shadow is again described (112) and the absence of contraction or the actual presence of systolic expansion has been demonstrated over infarcted areas of the wall (113, 114, 115).

The accuracy of indirect determination of cardiac output is dependent upon the methods used, and often results reported serve best to demonstrate the inadequacies of these methods. It is, therefore, not surprising that modifications of current methods continue to be described. The use of nitrogen (116) and of a modification of the Starr & Gamble ethyl iodide method for

quicker determinations of cardiac output were reported (117). The limit of the foreign gas methods was shown by the observation that in breathing a mixture of 20 per cent oxygen and 80 per cent acetylene, the arterial blood of the patient contained considerably less of the latter gas at the end of one-half minute than after three minutes (120). Improvements in the electromagnetic velocity flowmeter have been described (118, 119). The physical methods of calculating cardiac output designed by Broemser & Ranke and by Böger & Wezler, did not check too closely with such a direct physical method in rabbits (121, 122) or with the acetylene method in man (116). A method of calculating output from heart volumes determined by means of roentgenkymography was described (123) and it was found to check with the acetylene method except in incompetence of the heart valves. It is suggested that the greater value obtained in the latter case with the kymographic method indicates the regurgitant blood flow (123). The output of the heart calculated in relation to the heart size is decreased by a combined mitral stenosis and incompetence and even more so by a combination of both mitral and aortic stenosis and incompetence (124).

The relation of cardiac output to body surface in the obese was found to be within the normal range (125). A warm-adapted person after having previously been kept for a time at 32.4° C. had a decrease in cardiac output when kept for over a day in a room at 21.1° C. (126). Diet can alter cardiac output (127). A change of posture altered cardiac output (128) and the undertaking of exertion increased it (129, 130). The increase in cardiac output with work was 80 to 100 per cent, while the increase of heart size was only 8 to 13 per cent, suggesting that Starling's law is quantitatively modified in man under these conditions (129). The effect of work on cardiac output has been computed in terms of epinephrine equivalents (130).

In normal man the injection of 0.5 to 1.5 liters of normal saline or of five per cent glucose solution, at a rate of 20 cc. per min. had little effect on heart output, but faster rates increased cardiac output, venous pressure, arterial pulse pressure, circulating blood volume, and the velocity of blood movement (131). These changes outlasted the injection for ten to twenty-five minutes. The cardiac output was observed to increase in the pregnant woman, the uterus acting as an arteriovenous shunt (132). In the dog, by use of the

direct Fick method, it was found that renal hypertension did not change the cardiac output (133). After an operation under general anaesthesia, the cardiac output in man decreased 41 per cent, and one to four days were required for it to return to normal (134). Local anaesthesia, however, was followed by a temporary increase in output (134). The cardiac output was decreased in constrictive pericarditis (135) and in pleural effusion (136).

Cardiac output was decreased in experimental pulmonary embolism (137). A large pulmonary embolism exerts its effect by causing the dissipation of the right heart's energy in overcoming the obstruction (137); smaller emboli lead to a generalized pulmonary arteriolar constriction demonstrated by a rise in pulmonary arterial pressure (138, 139), produced apparently by means of an axone reflex (138). The coronary flow decrease which results from pulmonary embolism (138, 139) is apparently not a pulmono-coronary reflex (139), but presumably the accompaniment of the dynamic effect upon the right heart (137).

Hyperthyroidism (140), rapid or irregular heart action (141), and extremely slow rates (141) decrease the minute output of the heart. In heart failure, the cardiac output is usually decreased (103, 141, 142, 143), but not in all cases. Sometimes it is actually increased (141). However, when the cardiac output is computed per unit of heart size, a relative decrease is always apparent (141). When the heart fails, the increase in its output as a result of a standardized exercise is lessened (144).

The action of various chemical substances (145 to 152) and the effect of increased environmental pressure (153) on the magnitude of contraction in various animal species is reported.

A new type of pressure recording manometer utilizing a bubble of air in front of a photoelectric cell is described (154), as are several technical improvements in ordinary optical pressure manometers (155).

The dicrotic arterial pressure pulse is ascribed to resonance waves (156). Fever was found to change the contour of the arterial pulse (157). The pulse wave velocity accelerates from the aortic arch to the femoral artery but to varying degrees in different dogs (158). Vagus stimulation lowered this velocity beyond the expectation for the diastolic pressure level present; this suggests a change in elasticity of the aorta by virtue, perhaps, of an action by the vagi upon the smooth muscle tone of these blood vessels (158).

A similar type of elastic change appears to occur during acute hypertension in the dog; this outlasts the peripheral constriction (159). It manifests itself first as a decrease in aortic calibre and later by increased distensibility of the walls (159). In this study, Wiggers & Wégira used an ingenious aortagraph recording simultaneously with the pulse pressure record (159). Jochim *et al.* (160) used a special aortic oncometer for the same purpose. They found that increasing peripheral resistance had a variable effect on pulse pressure, but always increased the pulse volume of the aorta, indicating a relatively greater peripheral run off during diastole (160). Apparently peripheral resistance changes involve a dynamic flow factor which appears to be greater in systole than in diastole (160).

In a case of coarctation of the aorta, Hamilton *et al.* (161) found a difference in the arterial pressure pulses above and below the constriction indicating apparently independent elastic compression chambers. Pressor and depressor drugs also acted quantitatively differently on these two parts of the circulation. Hamilton & Dow (162) explored the changes in the pressure pulse along the arterial system from the aorta to the femoral artery in dogs and found that the pulse pressure increased toward the periphery. The peak of the pulse wave was shown to represent a stationary wave which occurred simultaneously throughout this stretch of artery. This peak was followed by alternate rises and falls which reciprocated with simultaneous pressure changes in the root of the aorta. The elastic compression chamber in dogs appears to go as far as the knee (162). As a result of their study, the conclusion is drawn that the concepts of reflected waves, standing waves, water hammer, and resonance are all related phenomena and not mutually contradictory (162).

The pulmonary arterial and venous pressures were explored in the unanaesthetized dog by angiostomy, and the changes under varying conditions suggest that these pressures reflect primarily the relative output of the two ventricles (163). In a human case with an aneurysm of the pulmonary artery, the pressure was determined by direct puncture and found to be 110 mm. Hg (164) which coincided with the calculated value by Schuntermann's method. This value is unduly high compared with a mean pressure of 20 mm. Hg found in the normal unanaesthetized dog (163,163a).

A modification of the method of direct venous pressure meas-

urement is described (165). The values obtained differ from those by indirect measurement by an amount of the order of the tissue pressure (165). The zero level in human venous pressure measurements should be considered to be 100 mm. anterior to the skin of the back in the supine position; this avoids errors dependent on differences in anterior-posterior chest diameter (166).

Energetics, Metabolism, and Chemistry

A new method of oxygenating the blood in the isolated heart preparation is described (167). Visscher (168) and Rühl (169) have presented data regarding the relative merits of their respective methods of measuring oxygen consumption of the heart. Burridge (170), on little evidence, has proposed a "new law of the heart."

Gollwitzer-Meier *et al.* (171, 172) found the energetics of the innervated heart-lung to be different from the denervated one. In the former, the work is done with less energy expenditure (especially when the load is increased), and the difference between the effects of increasing resistance and venous return are lessened. The oxygen utilization per unit of coronary flow is also increased. Epinephrine in the innervated heart results in less augmentation in oxygen consumption than in the denervated preparation.

Moe & Visscher (173) again reported that digitalis increases the efficiency with which the heart utilizes its energy for external work, and this is supported by another report (174). But Katz, Mendlowitz & Kaplan (175) obtained no evidence of any direct action by digitalis in therapeutic doses upon the cardiac size, output, oxygen consumption or efficiency; the view was held that digitalis action was secondary to its actions on the peripheral circulation (175). This last is supported anew (176).

The utilization of the effort during ejection was analyzed in man by Wiggers *et al.* (177) by the index of Wiggers and Katz, which is the ratio obtained by dividing the area of the arterial pressure curve during ejection above the diastolic pressure level, by the area between diastolic pressure and zero. In 81 normals this was found to be 0.215 to 0.880, being greatest in those with the larger pulse pressures and lower diastolic pressures. In 54 hypertensive patients the index was 0.220 to 1.030, and a large number were above the median of the normal group. The large pulse pressure in hypertension is the result of a decreased distensibility of aorta (177).

Visscher *et al.* (178) found that β-hydroxybutyric acid, when added to the blood of the dog's heart-lung preparation disappeared at a rate related to the blood sugar level and also related to the concentration of the fatty acid in the blood up to 100 mg. per cent. At this level 82 per cent of the oxygen consumption is held to be due to the fatty acid. The lung uses some of this. No acetone appears in expired air. The heart appears to use considerable quantities of this fatty acid; after discounting the blood and lungs, it is estimated that 20 to 80 per cent of the energy in these experiments was derived from the fatty acid (178).

Cruickshank *et al.* (179) found, on perfusing four rabbit hearts simultaneously for two hours without added sugar or buffer in the perfusate, that the adenylpyrophosphate content of the heart fell, and the creatine and inorganic phosphate content rose. In the second hour, the production of ammonia was detected suggesting the possibility that protein is the source of the noncarbohydrate material burned. In Lovatt Evans' laboratory (180) it was demonstrated that sodium pyruvate can be used by the heart in the heart-lung or isolated heart preparation, the extent of utilization depending on its concentration in the blood. It may be the source of noncarbohydrate fuel used by the heart, and it does not form glycogen in these preparations (180).

Profound anoxemia is required for the dog's heart to give up lactic acid to the blood stream (181). In the rabbit (182) and the rat (183) asphyxia and anoxemia cause the heart to lose 75 per cent of its phosphocreatine and adenosinetriphosphate and 90 per cent of its glycogen. This is reversible (182), but there is a lag in replacement of adenosinetriphosphate. The rate of decrease varies with heart rate (183). Hexosemonophosphate accumulates at the same time as the other substances disappear (182). The mechanical activity of the heart varies most closely with its phosphocreatine content (182). In rats trained for fourteen days, the losses of these substances during anoxemia was less than in untrained animals (183). Iodoacetate inhibited aerobic and anaerobic restitution of these substances in the rabbit's atrium (182). Under aerobic conditions, lactate, pyruvate, and phosphoglycerate led to the reaccumulation of the phosphocreatine, adenosinetriphosphate, and glycogen in the presence of iodoacetate; glucose, glycerophosphate, hexosephosphate, butyrate, valerate, malate, succinate, fumarate, and amino acids did not (182). Fluoride also inhibited the anaerobic recovery process of the rabbit's atrium (182).

Lovatt Evans *et al.* reported that after cyanide, or complete lack of oxygen in the respiration mixture, there was some disappearance of glycogen (184); epinephrine accelerated this loss. Exercise in rats, like anoxia, resulted in a decrease in glycogen, phosphocreatine, and adenylpyrophosphate (183, 185, 188); the rate of fall decreased with time. In trained animals the changes on exercise were less than in untrained animals (183). Diphtheria in the guinea pig did not decrease heart glycogen except when the heart was severely poisoned (186). Short periods of tachycardia in hyperthyroid animals did not alter the heart glycogen, but longer periods did so, especially in the left ventricle (187). Epinephrine decreased the glycogen of the heart more readily in the hyperthyroid heart than normally (187), and glucose did not prevent this. The phosphocreatine content of the heart was decreased by thyroxin (188), and thyroxin augmented the action of exercise in depleting the heart of glycogen, phosphocreatine, and adenylpyrophosphate stores (188).

The changes in blood lactate in heart failure (189) and under the treatment with caffeine and theophyllineethylenediamine (190) are described. The concentrations of histamine (191), of hydrogen ion, and of lactate ion are greater in blood from the coronary vein than in arterial blood (192). In ischemia of the heart, the arteriovenous difference of the latter is increased (193), and the potassium content of the coronary veins is increased (194). In shock the potassium content in the heart's blood of the cat is increased to 42.8 mg. per cent (195); in normal young adult man the blood potassium concentration is 17.2 mg. per cent; and in cardiac patients at death it was found to be 29.8 mg. per cent (195).

Little difference was observed in the glycogen content of the various chambers of the dog's heart, the left atrium and right ventricle having slightly higher values (196). Glutathione is lowest in concentration in the atria of the dog and highest in the left ventricle (197).

Electrical Manifestation of the Heart's Activity

The need for viewing the electrocardiogram as it is being written has led to the development of devices using either an endless belt of material of long persistent fluorescence or the cathode ray oscillograph (198, 199, 200).

Interest has reawakened in the recording of the cyclic movements of the manifest electrical potential in the heart cycle as

first suggested by H. Mann. For the most part the reports deal with the technique of recording and a descripton of the resulting vectorgraph in various two and three dimensional figures (201 to 208). The use of an esophageal lead continues and the records obtained with it are described (209, 210). Reports of human fetal electrocardiograms in limb or special leads applied to the mother still appear (211, 212) but are not convincing. Further reports have been made concerning the characteristics of the normal electrocardiogram in childhood (213, 214), in adults (215, 216, 216a), and in senility (217, 217a). The U wave appears to be part of the ventricular complex and the period when extrasystoles are most apt to occur (218).

The neurogenic origin of the electrocardiogram in the crawfish is noted again (219), and the characteristics of the electrocardiogram in circus elephants are given (220). The effect of posture (221, 222, 223), of exercise (222), and of transfusion and hemorrhage (223, 71) on the electrocardiogram are presented, as well as the effect in man of sympathectomy and sympathetic nerve stimulation (224), of uremia (225), of ketonuria (226), of acute nephritis (227), and of pericarditis (228). The effect of freezing (69), of hypercapnia (229), of alkali and acid salt ingestion (230), of potassium (231, 232), of magnesium (233), and of camphor (234) on the electrocardiogram are described. The independent variation of electrical and mechanical activity of the heart is noted again (235, 236).

The inequality of the electrical conductors which surround the heart has been confirmed (237, 238) and shown to apply to the animal with chest closed (238). The surface of the chest was explored in man, and it was shown that the semidirect lead concept was not valid, the changes in the electrical records being instead more properly attributed to a rotation of the electrical field in the body surface during the activation of the ventricles (239). The results support the view that the electrical manifestation of the heart's activity is the result of the action of a series of complex constantly changing batteries in a heterogenous electrical field (239). The field on the surface of the exposed heart was explored during the heart cycle and was found to undergo simultaneous variations in potential at various points with no clear distinction between the initial and final deflections (240). The electrocardiographic appearance of the QRS complex caused by injury to the

heart following aseptic coronary ligation in the dog was the same on the surface of and within the infarcted area as within the heart cavity (241); this indicates that the infarcted area acts as a "window," as it were, to the inside of the heart (241).

The genesis of the injury current was the subject of an extensive study by Eyster, Meek, *et al.* (242, 243) who reported that the potential changes seen on injury appear to be due to a new source of potential. When using the potential of resting uninjured ventricular muscle as zero, the potential of the injured region becomes positive during activity of the rest of the ventricle to a degree equal to or greater than its relative negativity during rest. Differential electrodes show an absence, complete or almost complete, of activity in the injured area (242). By exploring the surface of the heart, this new source of electrical current can be resolved into two concentric rings at the junction between the injured and uninjured areas; the one toward the injured area being negative, the other positive (242). This injury current is not due to contraction of the heart since it occurs in its absence (243). It is dependent on activation of the muscle surrounding the injured area, since functional separation of an injured auricular appendix did not produce the positive phase during activity seen before this separation (243).

An attempt was made to verify the "indifference" of various distant electrodes when exploring the body surface near the heart. For this purpose the patient was immersed in a salt bath in a metal tub with a metal cover (244, 245). The metal tub and covering were used as the indifferent electrode. This permitted a better exploration of the characteristic spatial distribution of the electrical field on the body surface than could be obtained by calculations of electrical axes or by vectorgrams (245). On theoretical grounds even this indifferent electrode does not remain at zero potential during the heart cycle (244). This is shown to be true also of both the Wilson's indifferent electrode and the distant limb electrode, although they remain practically usable. Einthoven's law does not hold when an equilateral triangle is mapped out on the anterior chest wall in ten out of twenty patients tested (246).

Physical Manifestations of the Heart Activity

Several modifications of methods of observing heart sounds have been described (247, 248). The presence of four normal

heart sounds has been emphasized and recorded (249, 250); the first of these is atrial in origin and can be recorded distinctly during atrial activity in complete atrioventricular block (251). The presence of functional systolic murmurs in a normal heart (252, 253) and even of functional diastolic murmurs (254) are reported.

The square root formula of Lombard & Cope and the cube root formula of Fridirica are still widely used in correlating systole duration to cycle length. Several modifications have appeared: Ashman (255) proposes

$$S = K \log[10(C+k)]$$

where S = duration of electrical systole in seconds, C = cycle length in seconds, $K = 0.373$ to 0.385, and $k = +0.07$; Sebastiani (256) suggests

$$S = \frac{C}{10} + 22.2$$

and Lian & Baraige (257) offer

$$D = KC(C+41)$$

where D = duration of diastole, $K = 0.0040$ to 0.0049, and C has the same meaning as in the first formula. These formulae have been tested on normal groups of patients by their proponents and found by them to give a better fit than did earlier formulae.

The action of various procedures and drugs on the relative duration of electrical systole has been reported (58, 157, 258 to 268). In damage by diphtheria (269) and usually in heart failure (270), systole is relatively lengthened, although in some instances of severe heart failure it is shortened (270). Digitalis also shortens the relative duration of systole (264).

Several new substances for determining circulation time have been proposed. Thus, the intravenous use of 0.5 cc. of acetone in 1 cc. normal saline was suggested, the end point being the appearance of acetone in the breath as shown by the iodoform test (271). With this method the time in normals is 8 to 10 sec. (271). Fifty per cent carbon dioxide in two inhalations results in a sensation of warmth and increased respiratory effort in 5 to 10 sec. in normal subjects (272). Cough following 1.4 cc. of paraldehyde injected intravenously occurs normally in 3 to 9.5 sec. (273). Lobelin injected intravenously (0.03 to 0.07 mg. per kg.) also

causes a cough and has been used to measure circulation time, the average normal time being 10 to 10.5 sec. (274, 275). When several cubic centimeters of magnesium sulphate in a 10 per cent solution are given intravenously, a sensation of warmth develops in 7 to 17.5 sec. in normal subjects (276). The fact that circulation time is abbreviated in hyperthyroidism (272, 275, 277) and prolonged in heart failure (271, 272, 275, 277) was confirmed. That changes in circulation of the limb affects the circulation time was shown during postural changes (278) and by establishing a difference of temperature in the two upper extremities (279).

The lure of finding a functional test for the cardiac state continues, despite the fact that none has as yet met expectations. Several reports dealing with this subject have appeared (280, 281, 282).

Innervation

Confirmation of the role of the reflex control exerted by the carotid sinus and aortic moderator mechanisms upon the heart are reported for the experimental animal (283, 284, 285) and for man (286, 287). Some of the efferent fibers involved in this control are extravagal; they were found to have about eight per cent of the effect of the vagi (285).

The stellate ganglion of the dog contains cardio-inhibitor fibers which arise in the vertebral nerves and upper dorsal rami communicantes (288); these are analogous to the cardio-accelerator nerves found in the vagi, the presence of which have been again confirmed (289). This last was accomplished by studying cardiac acceleration in completely sympathectomized cats following exercise or emotion (289). The acceleration in sympathectomized cats amounts to thirty per cent of that in the normally innervated animal (289). In the sympathectomized dog, vagus tone reappears postoperatively after twenty days so that an acceleration can be again produced with atropine (290). This is held to indicate that this vagus mechanism lies dormant when sympathetics are intact (290).

In the frog the vagus fibers go to the ventricle (291). In the dog they go to the idioventricular pacemakers (292), and this appears to apply to man also (293). Fredericq has continued his studies on the properties of the vagus to repetitive stimuli (294), and Chauchard (297) has studied its chronaxie as well as that of the sympathetics. Gruber *et al.* (295, 296) have demonstrated that

phenobarbital acts in part upon the vagus nerve, its intracardiac ganglia, and its pre- and post-ganglionic fibers. Simultaneous stimulation of vagus and sympathetic nerves shows an additive effect of their individual actions (298).

When acetylcholine administration and vagus stimulation are carried out simultaneously, their combined effect on the dog's heart is more than additive, but vagus stimulation after acetylcholine has less than its usual effect (299). This is true also of giving acetylcholine after vagal escape (299). The inference is drawn that a mechanism is set up which accelerates acetylcholine destruction; this is supported by work on the frog concerning the escape of the heart from continuous slow acetylcholine perfusion (300, 301) and by the fact that the concentration of acetylcholine perfusate is diminished on passage through the heart (302). Acetylcholine is liberated in the heart in the absence of nerve stimulation (303); Lissák (304) has demonstrated that the addition of calcium results in the liberation of an adrenergic substance in the frog which has a positive inotropic action when perfused through a second frog's heart; it resembles Loewi's sympathetic substance. The dioxane derivative, 933F, abolishes the action of sympathin in the frog but has no effect on sympathetic nerve stimulation (305). This is attributed to an *in vitro* destruction of 933F (305). However, 933F is reported not to effect the response of frog and cat hearts to epinephrine and to sympathetic nerve stimulation (306), but this is out of line with its actions in other regions and is difficult to understand.

Coronary Flow

Schlesinger (307) has shown clearly by an ingenious technique that the coronary arteries are normally true end arteries; anastomoses between vessels occur only when one of the vessels is occluded. Repeated injection of large quantities of acetylcholine into rats (308) and into rabbits (309) led to coronary sclerosis and myocardial fibrosis. In dogs similar results were obtained from parasympathetic overactivity (308). Insulin shock in rabbits, contrary to previous reports, did not cause focal necrosis (310).

Modifications of the Langendorff isolated heart perfusion are described (311, 312). Several new devices for measuring coronary flow are reported by Gregg & Green (313, 314, 315), and by means of these it is shown that the differential manometer gives the direction of flow changes in the coronary vessels but not their

true quantitative relationships (316). In the anesthetized animal coronary flow is faster than in the unanesthetized one (317).

The coronary flow in surviving beating human hearts of patients who had died in heart failure were studied by Kountz (318) and found to be 0.15 to 0.6 cc. per min. per gm. of heart, which is low as compared to 1.4 cc. per min. per gm. of heart in surviving "normal" hearts. The lowest values in the failing hearts were obtained when coronary sclerosis was present (318). The differences are ascribed to dilatation of the heart, to coronary sclerosis, and to cardiac hypertrophy. The action of drugs on coronary flow in dilated hearts may be the reverse of that in normal hearts (318). Katz *et al.* (319) have shown that the manner of beating of the heart plays a definite role in determining the rate of coronary flow; increasing contraction diminishes the inflow into the coronary arteries and increases coronary sinus outflow. The view that the coronary sinus flow forms a variable proportion of the coronary drainage established in this study has been confirmed (320, 321, 322). This fluctuation according to Moe & Visscher (322) appears only when the difference between the mean aortic and pulmonary arterial pressure (in the heart-lung preparation) is less than 40 mm.; at greater pressures the ratio of coronary sinus outflow to total coronary inflow is practically constant.

The necessity of taking into account the variability in the quantity of blood in the coronary vessels in estimating small changes of oncometric diastolic volume is emphasized (323). The pattern of coronary flow partition is variable and so is its drainage in different individual dogs (320). There is little drainage (less than 10 per cent) of coronary blood into the left heart (320). The intramuscular pressure in the left ventricle during systole as determined by an ingenious method is a variable, depending upon the depth within the heart wall at which the measurement is made (324). This fact can influence the coronary flow, so that the cyclic fluctuations are different in the various intramural coronary vessels.

Aortic stenosis, suddenly produced, causes ischemia of the musculature in the middle of the ventricular wall (325). In aortic insufficiency the ischemia is said to be diastolic only (325). The decrease in coronary flow in those two valvular defects was demonstrated experimentally and shown to be independent of the aortic pressure (326); it involved both systolic and diastolic flow.

Increasing the work of a trained dog results in an increase in coronary flow as measured by a stromuhr previously applied to a coronary artery, and this flow is not entirely dependent upon blood pressure, but is best correlated with the changes in heart rate (327). The effect of various drugs on coronary flow has been studied in the isolated heart, in the heart-lung preparation and in the intact animal, and both by direct measurements of coronary sinus outflow or of flow in one of the coronary arteries, or indirectly (317, 328 to 337). The results with these various methods are surprisingly in accord. These changes are not always dependent upon the changes in aortic blood pressure (328, 331, 333, 335, 337), but this effect varies with the drug used. Katz *et al.* (338) have developed a preparation whereby the effects of such drugs upon the tone of the coronary vessels can be measured directly, permitting the determination of the extent to which such active changes in coronary caliber contribute to the changes in coronary flow. The most powerful constrictors by this method were found to be pitressin, potassium, and the blood of foreign species (338, 339, 340). This last is in agreement with the action of anaphylaxis in certain species (341). A species difference in the response to these various chemicals exists (338, 341). The action of epinephrine on coronary flow is no different in the innervated than in the denervated heart-lung preparation of the dog (172).

Digitalis was shown not to alter the coronary flow in the trained (342) and in the anesthetized animal (343) until toxic doses are reached, at which time a decrease occurred. This decrease with toxic doses appears to be parallel to the decrease in cardiac output (343). The decrease in coronary sinus outflow previously found to result from administration of digitalis is confirmed (344), but this is not a contradiction since coronary sinus flow can vary in the opposite direction to coronary inflow (319).

Contrary to the generally accepted view, Katz & Jochim (345) have shown that the vagi of the dog carry only cholinergic coronary vasodilator fibres, while the sympathetics have both adrenergic vasoconstrictors and adrenergic vasodilators. These are all tonically active, and in the sympathetics the constrictors predominate.

That anoxemia produces changes in the electrocardiogram similar to those associated with ischemia in animals (346) and in man (347, 348) is confirmed. This has been used as a method of testing the efficacy of drugs in altering coronary flow in man (348). Injury

near the apex of the heart appears to have a predominant effect in producing injury currents in the electrocardiogram (349). Injury to the atria distorts the atrial deflection (350).

The specific changes in the electrocardiogram in infarction are determined by which of the four muscle bundle groups is involved, according to Robb & Robb (351). This is based on a necropsy correlation (351). Their concept that injury may be limited to muscle bundle groups is supported by another independent investigator (352) but is not widely accepted. The concept that injury to surrounding living tissue and not the presence of dead or necrotic tissue is the cause of the electrocardiographic changes is concurred in on the basis of anatomical studies (353, 354).

Asphyxia and anoxemia result in an increase in coronary flow (354a), as do hypercapnia and acidemia (355). This, Katz & Lindner (356) have shown, is actually due to active dilatation of the coronary vessels, resembling reactive hyperemia elsewhere.

The hypodynamic state of the heart following coronary occlusion is again reported (357, 358, 359, 360), and the view that the mechanism is a loss of power within the heart and not a reflex peripheral collapse is supported by further evidence (358, 359). In this, as in all conditions of sustained low blood pressure, irreversible shock may eventually occur.

The work of F. M. Smith and his collaborators purporting to show that aminophylline tends to reduce the size of the myocardial infarct following experimental coronary occlusion is not supported by the results of Gold *et al.* (361). The dynamic effects of acute coronary sinus obstruction or ligation have been carefully studied by Gregg & Dewald (362, 363) and found to be such as not to warrant its use to counteract the effects of coronary arterial occlusion. The dynamics of chronic slowly developing experimental coronary occlusion in animals has been investigated (363, 364, 365, 366). The use of cardiopexy first developed by C. Beck has been thoroughly analyzed and the development of an enhanced coronary flow again demonstrated (366a, 367). Stellate ganglionectomy in the dog did not affect the dynamic results of coronary occlusion, but the immediate mortality and the occurrence of ventricular fibrillation was lessened (368).

The finding is confirmed that mechanical procedures involving stretching of the coronary vessels of the dog lead to affective responses such as are seen when painful stimuli are applied (369).

Intramuscular injections in man suggest that the chemical factor responsible for muscular pain, and inferentially for anginal pain, is not potassium or lactate, since these substances do not show additive effects with ischemia of the muscle (370). Experimental studies on patients with a history of angina pectoris show that their appreciation of pain in response to sensory stimuli set up in the ischemic left arm tends to show spatial summation (371).

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CARDIOVASCULAR DEPARTMENT
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BIOELECTRIC POTENTIALS

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The present review, which covers the literature to September, 1939[1] deals to a large extent with the same subject matter as did the corresponding chapter in the first volume of this series (33). The risk of some duplication must, however, be taken because in the past year there has appeared much new material which is concerned with the electrophysiology of nerve, muscle, the myoneural junction, the synapse, and the nerve cell, and because steady progress has been made in the clarification and the extension of the interpretations of electrophysiological data. Furthermore, differences which are inevitable among different experimenters in the points of emphasis and their degree will, it is hoped, keep the duplication at a minimum.

The form of the action potential.—Recent data (16, 75, 89) favor the view that nerve fibers of mammals divide themselves into three groups, each of which is characterized by its action potential. According to the current nomenclature (59), the different groups are called A, B and C, which in the cat and rabbit have the properties enumerated in the table on page 214.

The various groups overlap with regard to properties such as velocity, diameter, and duration of the absolutely refractory period and of latent addition. They overlap also with respect to threshold (16, 89). The elements of the action potential, namely the spike and the after-potentials, are then the chief specifically characteristic properties of the nerve fibers. Closer investigation, however, reveals that the action potentials of the three fiber groups show fundamental similarities, which have been generalized by a schema developed by Gasser (67). According to this generalization, in all three groups the action potential is the resultant of a spike negativity followed by a sequence of negative and positive after-potentials.

All the components of this sequence are visible in the action potential of mammalian autonomic C fibers (90), where the spike

[1] References will be made in footnotes to several important papers which appeared too late for critical review.

is succeeded by a negative after-potential, which in turn is followed by a positive after-potential composed of two elements, P_1 and P_2. The first positive potential, P_1, lasts about 300 msec., and since it is increased when the spike activity is augmented, it appears to be related to spike production; the second positive potential, P_2, is present to a variable extent in the single response and, being conditioned by the amount of antecedent activity, is an extension of the negative after-potential.

TABLE I*

Properties of three Groups of Mammalian Nerve Fibers

Group	A	B	C
Diameters of fibers, μ	20 to 1 (75, 107)	<3 (89)	unmyelinated
Conduction velocity, m.p.s.	100 to <5 (75, 107)	14 to <3 (89)	<2 (90)
Spike duration, msec.	0.4 to 0.5 (75)	1.2 (89)	2.0 (90)
Negative after-potential *Amount*, per cent of spike *Duration*, msec.	 3 to 5 (74) 12 to 20 (74, 118)	 None (89) —	 3 to 5 (90) 50 to 80 (90)
Positive after-potential *Amount*, per cent of spike *Duration*, msec.	 0.2 (74) 40 to 60 (74, 118)	 1.5 to 4.0 (89) 100 to 300 (89)	 1.5 (90) 300 to >1000 (90)
Absolutely refractory period, msec.	0.4 alpha (74, 75) 0.6 delta, cat (75) 1.0 delta, rabbit (75)	1.2 (89)	2.0 (90)
Period of latent addition, msec.	0.2	0.2 (89)	2.5 (89)
Order of susceptibility to asphyxia (89)	2	1	3

* Figures in parentheses give the references.

In mammalian A fibers (74), P_2 is absent in the single response, while in frog A fibers (72), all positivity is usually absent and the action potential is represented only by a spike followed by a negative after-potential. In frog C fibers (76) and in mammalian B fibers (89), the single response is characterized by an action potential that is composed only of a spike and a relatively large positive after-potential.

In all these nerves, although the action potential is distinctive for each group, the presence of all the components of Gasser's schema can be demonstrated by special methods of study or by appropriate experimental procedures (1, 2, 64, 74, 76, 78–86, 89, 90). The after-potentials of the three groups differ, therefore, only quantitatively in the relative magnitudes and time scales of the three components.

Comparable correlations are not available for the potentials of invertebrate nerves, but positive and negative after-potentials do exist as elements of the action potential. References to earlier work are given by Arvanitaki (4), who also describes the supernormality that is associated with the negative after-potential (pp. 101 ff.).

Especially noteworthy are two points derived from the table. The spike duration is constant for all mammalian A fibers within the limits of 0.4 to 0.5 msec. and is, therefore, independent of the size of the fibers, while the absolutely refractory period is not independent and increases for the smaller fibers.

A number of the properties of nerve fibers are correlated with the size of the fiber. Nerve fibers enlarge during the fetal and postembryonal development of the animal (50). In four-day old kittens the maximal velocity at which the impulse is conducted in the saphenous nerve is 11 m.p.s. (108), as compared with 80 to 90 m.p.s. in full-grown cats. As the kitten grows, the maximal velocity increases at a rate directly proportional to the diameter of the largest fibers ($V \sim D$). This linear relationship between the diameter and the velocity also holds for the largest fibers of the nerves of the full-grown cat (107) and applies closely for the entire range of myelinated fibers in the saphenous nerve of the cat (16 to 1 μ) and the rabbit (12 to 1 μ), and in the phrenic nerve of the cat (14 to 1 μ) (75).

The relation, $V \propto D^2$, has been advocated by Blair & Erlanger (19) on the basis of data obtained from the phalangeal preparation of the frog, and by Zotterman (160) from his experiments on the saphenous nerve of the cat. In both cases, however, the measurements actually made were of the relation of the amplitudes of the recorded axon potentials to their velocities of propagation. Both sets of data show an approximate linearity in this relation ($P \propto V$). In deriving from this experimental finding the relation of $V \propto D^2$, the investigators based their conclusion on the original premise of

Gasser & Erlanger (71) that the recorded axon potentials are proportional to the square of the diameter ($P \propto D^2$). Gasser & Grundfest (75) have, however, called into question the earlier hypothesis of Gasser & Erlanger and have suggested that the recorded potential is in approximately linear relation to the diameter of the active fiber ($P \propto D$), a conclusion which is founded on both experimental evidence and theoretical considerations. This new formulation reconciles the direct experimental measurements made on vertebrate fibers of the linear relation of the velocity and the diameter ($V \propto D$) (75, 107, 108), with the data on the linear relation of the velocity and the potential ($V \propto P$) (19, 75, 160).

Over the much wider ranges of fiber diameter that are available in cephalopod nerves (700 to 30 μ) measurements of the velocities (136) at which they conduct yield the relation: $V = KD^{0.641}$, but because of the scatter of the data, $V = KD^{0.5}$ gives almost as good a fit. The relation, $V = KD$, which fits quite well for the smaller nerves of vertebrates (20 to 1 μ), does not give as good a fit as either of the others, while $V = KD^2$ gives the poorest fit.

On the basis of (1) a spike duration that is constant for all A fibers, (2) the linear relation between the recorded axon potential and the axon diameter, and (3) an empirically determined and approximately linear relation between the velocity and the axon diameter, Gasser & Grundfest (75) have reconstructed the recorded spikes of saphenous nerves of the cat and the rabbit and of the phrenic nerve of the cat from measurements of the distribution according to size of the myelinated fibers of these nerves. The reconstructions reproduce with a high degree of accuracy the elevations developed by the A fibers and recorded from the same nerves.

Myelination of the axon takes place as the fiber enlarges above a critical diameter in the developing animal (50). In the nerves of fully grown animals, the ratio between the diameter of the axon and the outside diameter of the myelinated fiber does not stay constant (3, 75, 146) at the value of 0.7 given by Donaldson & Hoke (47). In paraffin sections of the osmic acid preparations of the saphenous nerve of the cat (75), that ratio holds for fibers with outside diameters greater than 8 μ, but, for fibers having diameters below that value, the ratio falls continuously, to become 0.55 at 3 μ.

That chronaxie is greater in small fibers (19, 117) has been ob-

served in nerves of the squid (135). The absolutely refractory period likewise is longer for smaller fibers (19, 75, 107). In form the functions are apparently similar, and over a large range of fiber sizes both the chronaxie and the absolutely refractory period remain essentially constant, and then increase rapidly for small fibers.

The correlation between the excitability cycle and the sequence of after-potentials that exists in large A fibers (74) holds also for other nerve fibers. After a single conditioning action in the small A (δ) fibers (75) and in the autonomic C fibers (90) of the cat, supernormality exists during the negative after-potential and is succeeded by subnormality with the onset of the positive after-potential. In bullfrog C fibers (76) and in mammalian B fibers (89), in keeping with the absence of negative after-potential, there is no supernormality; but a peak in the subnormal excitability indicates the existence of a supernormality that is submerged, just as is the negative after-potential.

Fiber type and function.—While the A and C fibers mediate both sensory and motor activity, the B fibers are known only in the preganglionic nerves of the autonomic system and probably also in the postganglionic ciliary nerves (89). The sensory function of mammalian C fibers was shown by Clark, Hughes & Gasser (41) and confirmed by Bishop & Heinbecker (14), and more recently by Zotterman (161). The last mentioned investigator has also made a number of correlations between the types of sensory stimuli and the velocities of the afferent impulses, and hence also the sizes of the conducting fibers. Zotterman's data confirm in the main the earlier findings [which are summarized by Gasser (65, 66)] that sensory fibers of a wide range of diameters are activated by many forms of sensory stimuli. A new finding in his work is the fact that the delta fibers carry afferent impulses evoked by light touch.

An interesting correlation between size and function is the observation of Hursh (108) that in the nerves of kittens the velocity of the nerve impulse over a wide range is directly proportional to the length of the leg, so that the conduction time at the various ages is nearly constant.

The frequency of afferent stimulation may determine the character of the response (7). At high frequencies of stimulation there is produced an increase, and at low frequencies a decrease in the blood pressure. A similar phenomenon has been observed (92)

for the effects of the stimulation of the hypothalamus. The responses that were modified by the changes in the stimulating frequency were the blood pressure, the respiratory rate, the amount of after-discharge, and the pupillary and postural reactions.

A distinction that has recently been made between the sensory and the motor nerve fibers is in the report (115) that sensory fibers degenerate more slowly than do the motor fibers. Another distinction is found in the absence of acetylcholine in the dorsal roots (123).[2]

The multiple innervation of invertebrate muscle fibers and inhibitory nerve fibers of crustacea.—A problem which deserves the increasing attention of physiologists is that of the innervation of the muscles of arthropods. In the leg muscles of crustacea, Wiersma, van Harreveld, and their associates (95) find two to four motor fibers and one inhibitory nerve fiber innervating the same muscle. Often all the nerve fibers branch at the same level. Van Harreveld (93, 94) has concluded that each muscle fiber is multiply innervated by all the fibers in the nerve bundle. Young (159) reports that the muscle fibers of the squid are also multiply innervated.

In the leg of the cockroach, two motor fibers innervate the muscles and no inhibitory nerve is found (134). One of the motor fibers on stimulation causes a rapid twitch-like response of the muscle and the other a slower, smaller contraction. Upon repetitive stimulation of the "fast" fiber, the muscle responds with a series of discrete maximal twitches. With a similar stimulation of the "slow" nerve fiber, the response is a smoothly growing contraction. In the crustacea, stimulation of the "fast" fiber causes a large twitch and a large action potential, and of the "slow" fiber, a small contraction and a small action potential (157). Under some conditions, repetitive stimulation of the fast fiber produces action potentials in the muscle, but no contraction; while at the same time a contraction is developed in response to stimulation of the "slow" fiber and is accompanied by the small action potentials. Wiersma & van Harreveld believe, on the grounds of these data, that the two nerve fibers set up in the same muscle fiber different excitatory changes up to and including the development of different types of muscle action potentials. The two independent but

[2] Hellauer, H., and Umrath, K., *Z. Biol.*, **99**, 624 (1939); Chang, H. C., Hsieh, W. M., Lee, L. Y., Li, T. H., and Lim, R. K. S., *Chinese J. Physiol.*, **14**, 27 (1939).

parallel excitatory systems then end in the contraction as a final common path (158). The transmission mechanism of the muscle fiber is also presumed to be secondary to the action of the nerve fibers, which are supposed to activate the muscle fiber at a number of loci. A different explanation has been proposed by Pringle, namely, that the twitch-like response is attributable to the simultaneous activation of all the muscle fibers by the "fast" nerve fiber; while the "slow" fiber is at first able to stimulate only a few muscle fibers, but that on repetitive stimulation a progressively increasing number is activated. Pringle also makes an interesting comparison between the functional arrangements which he finds in the cockroach and those that obtain in the crustacea.

What appears to be a fact contrary to the theory of the multiple innervation of the muscle fibers is the observation (95) that simultaneous stimulation of three motor nerve fibers produces a contraction which is the summation of the effects produced when the nerve fibers are stimulated individually. Neither the action potentials of the nerve fibers nor the physiological properties and the intimate anatomy of the muscle fibers are yet known, and a definitive description of the physiological mechanisms that apply to the nerve-muscle system of these invertebrates is not at hand.

The mode of action of the inhibitory fibers is not clear. Where a number of motor fibers are available, stimulation of the inhibitory fiber produces different effects upon the characteristic muscle response caused by the stimulation of each motor fiber. Stimulation of the inhibitory fiber alone produces no action potentials in the muscle, but does leave behind effects upon the responses to subsequent motor stimulation (129). Marmont & Wiersma suggest that the action of the inhibitory nerve fiber is to interpose a block in the transmission between the excitatory system—in which is included the action potential—and the contractile system of the muscle.

In the clam (137) two types of spikes have been recorded from the mantle nerves. A large spike is associated with a twitch of the retractor muscle, while there is also a small spike which may be associated with a small or with no muscle response. Pumphrey believes that the effect of the nerve fibers producing the small spikes is an influence on the motor response produced by the other type of nerve fiber, similar to the action exerted by the autonomic fibers of vertebrates in the Orbeli effect.

Experimental modification of the action potential: spike height.—In C fibers the spike height is increased during the positive after-potential resulting from previous activity (76, 90). A similar modification is produced by anodal polarization, and the reverse is caused by cathodal polarization (83).

Extinction of the spike by asphyxiation.—The B fibers in their sensitivity to asphyxia fall into line with the mammalian A fibers; the former are more easily asphyxiated than are the most sensitive A fibers (the delta group) (89). C fibers, on the other hand, are the most resistant (41).

Polarization by external currents.—Graham (83, 84) has studied the modifications produced in the spike and the after-potential by polarization. At the anode, weak polarizing currents increase the spike and both negative and positive after-potentials of C fibers. With stronger currents, the effect on the negative after-potential outweighs the changes in the positivity, giving in A fibers the appearance of decreasing the latter. Cathodal polarization, by removing the negative after-potential, increases the recorded positivity; the curves of recovery and of latent addition are also modified by polarization (17).

Effects of pH.—Since the work of Lehmann (118), a standardized technique is available for maintaining mammalian nerves under reproducible conditions. For an environment approximating closely that of the body, the nerves are bathed in Krebs' modification of Ringer's solution in an atmosphere of 5 per cent carbon dioxide and 95 per cent oxygen. Changes in the pH are easily accomplished by changing the amount of carbon dioxide in the gas mixture.

As in A fibers (118), a decreased pH increases and prolongs the negative after-potential of C fibers (90) and develops in B fibers a negative after-potential where none existed before (89). C fibers are slightly sensitive to increased pH, while the B fibers are extremely so. Immediately upon producing a change of the gas mixture to give a pH of about 8.0, the positive after-potential of the B fibers of the cat shortens from a value of 100 to 300 msec., to one of 60 to 80 msec. The change is fully reversible.

The effect of drugs.—A description has recently been given of the effects of strychnine (96). This drug lowers both the spike and the after-potentials of C fibers, but the concentrations necessary are rather high. Concentrations exceeding 1×10^{-6} raise the thresh-

old of nerve. A remarkable effect is the slowing up of accommodation and the increase in the period of latent addition.

The threshold of nerve to electrical excitation is heightened in conditions which increase the negative after-potential, and lowered by factors which increase the positive after-potential (88, 97, 118). Whether there is a direct correlation between the resting threshold and the type of after-potential response is unknown. An ingenious correlation has been made between the effect of agents upon the electrical threshold of nerves and their effectiveness in modifying the frequency of spontaneous discharge (31). Procedures that increase the frequency of impulses, e.g., decreased calcium ion concentration, would have reduced electrical thresholds in normal nerve, and *vice versa*. It is interesting to note that the same agents which modify the after-potential, the threshold, and the degree of rhythmicity in the response, also modify the degree of accommodation (98, 149), and that this modification can be correlated temporally with the onset of the change in the degree of rhythmicity of the response (148).

Polarization and changes in the chemical environment also effect modifications in the persistence of the heightened excitability that follows upon a sub-threshold stimulus (17, 130), as has already been pointed out by Gasser (69). Of particular interest is the fact (130) that a decrease in ionized calcium, which causes an oscillatory type of after-potential sequence, also produces an oscillation that was first seen by Erlanger & Blair (61) in the persisting excitatory state which remains behind after a sub-threshold stimulus.

The disappearance of the local excitatory state and of accommodation, both of which are involved in the process of excitation (98), thus seems to be affected by the same agents. Since the decay of the excitability after a brief sub-threshold stimulus, according to Hill (98), is compounded of these two processes, the curve of latent addition may take several forms (59, 81, 87). Its spatial modification (125) may depend not only upon the spreading electrotonic current, but also upon the local modifications produced in the two factors involved in excitation. In the C fibers of both the frog and the mammal, accommodation is insignificant (unpublished data). This situation makes it possible to stimulate C fibers in mixed nerves without exciting fibers of the other groups (16).

If bioelectric potentials accompany the relatively long-lasting changes in the excitable state, they have not yet been demonstrated in the nerves of vertebrates. Evidence has been presented that the "*ondes lentes*," which sometimes prelude activity in crustacean nerves, may be of this nature (4, 62). The depolarization which may precede or accompany the activity of cells (4, 10, 96) has been discussed in the previous volume (33).

That bioelectric potentials do accompany and can cause brief changes in excitability has been definitely established. Direct evidence obtained by electrical recording that potentials accompany sub-threshold excitation has been presented for crustacean nerves (5, 102), in the plant *Chara* (8), and in the muscle end-plates of the frog (77)[3] and the cat (53). In the pallial fibers of *Sepia*, Arvanitaki (6)[4] finds that not only is there a local response ("prepotential") preceding the conducted spike, but that during the application of a sub-threshold constant current, a series of such "prepotential" responses is evoked. Indirect evidence of the existence of a potential accompanying sub-threshold changes of excitability has been presented also for the nerve fibers of the frog (111), but the possibility of their existence has been denied (18). There is reason (102) to believe, however, that the expectations of recording such potentials in a multi-fibered preparation of myelinated nerves are very small.

The discovery of the local response in nerve is of particular interest because it represents a successful prediction based upon the mathematical treatment of nerve as a network with properties similar to the electric cable. According to these deductions (141, 142), local action potentials may be set up, but the impulse, because the segment of nerve activated is too small, will fail to propagate. The local response obtained by Hodgkin in single crab fibers is indeed of this nature (102). It represents a local cathodal depolarization, which can be propagated to a small extent and which sets up a refractory period. The local response grows rapidly, with increase in the strength of the stimulus, and at threshold it reaches about twenty per cent of the spike, which in these single fibers may attain 60 mv. At threshold there may or may not be a response set up, depending upon the well-known play of responsiveness (59), and the response may originate at

[3] Schaefer, H., and Haass, P., *Arch. ges. Physiol.* (*Pflügers*), **242**, 364 (1939).
[4] Arvanitaki, A., *Arch. intern. physiol.*, **49**, 209 (1939).

the cathode or it may be set up by active electrotonic propagation of the local response in another, more excitable region of the nerve.

The electrotonic propagation of currents imposed on the nerve has long been known (23). The time course of these changes has recently been studied in nerve (125, 126) and in muscle (145) and correlated with the core conductor theory. The electrotonic spread of the bioelectric current set up by activity also causes a subthreshold increase of excitability which may be summed with and is entirely like the electrotonic modification of excitability (100, 101, 126, 153). Hodgkin (101) has also calculated from his experimental data the potential ability of the local bioelectric circuit to excite a new region of the nerve and thus to propagate the impulse. His calculations indicate that the local circuit set up by an impulse is more than sufficient to reexcite a new region and that the "safety factor" is of the order of three to ten. Tasaki (153) has made a similar calculation from experiments performed on the very excellent material that has been developed by Kato and his coworkers (110, 151), the single nerve fiber-muscle preparation of the Japanese toad. From the ability of the nerve impulse to jump across at least two nodes, made inexcitable by narcosis, an experiment which confirms that of Blair & Erlanger (20), Tasaki calculates the safety factor as eight to ten in freshly excised nerves. In the same paper are discussed the conditions which may affect the safety factor and the role that it may play in the recovery from refractoriness. Tasaki suggests that the recovery of the safety factor is represented by the return from absolute refractoriness. This suggestion is in line with the observation made in mammalian A fibers (74) that at the stimulating cathode considerable potentials are recorded at very high rates of stimulation, while conducted spikes are not observable.

On the basis of the theory of a simple electrical network, Tasaki also calculates that the electromotive force of an active frog fiber is of the order of 100 mv. That this large value is not impossible is evidenced by the similar results of Gasser's calculation (68) from the approximate differences in the ionic concentrations on the opposite sides of the nerve membrane, and still more from the actual recording made by Hodgkin (102) of single spikes about 60 mv. large in the single nerve fibers of the crab preparation.

Other calculations of the safety factor are available. From data on the electrotonic spread of current in frog muscle, Schaefer *et al.*

(145) have calculated a high safety factor for the excitation of a muscle fiber by the nerve impulse. A different result is, however, obtained from the data of Cole & Curtis (42) on the impedance changes that occur during activity in the giant fibers of the squid. In these important experiments it was found that the capacitative component of the impedance changed only slightly (about two per cent), while the resistive component fell from 1000 ohms cm.^{2} to 25 ohms cm.^{2} during the passage of an impulse. The spike developed at the locus at which the impedance changes were measured was also obtained, and the time course of the potential change and of the impedance change were compared. Since the spike is complicated by the recording, through electrotonic spread, of more distant potential changes, while the impedance change probably reflects events near the point of testing, the impedance curve represents the time course of the local activity more accurately than does the spike. The direct comparison of the potential and of the impedance data should, therefore, give the size of the electrotonic potential which is needed to initiate activity at the recording locus. The Lissajous figure produced by the simultaneous recording of both changes during the passage of an impulse (42, fig. 11) shows that the onset of the impedance change occurs when the rising action potential has reached its inflection at about half the full value. The safety factor in the giant nerve fibers of the squid would accordingly be two.

Whatever may be the exact magnitude of the safety factor, there is evidence that the passage of an impulse may set up further propagated activity (4, 9) and that a spike, when it arrives at a regional block, may stimulate the nerve fiber beyond the block either by electrotonic spread of the bioelectric current (20, 153), or even by the application of this current through a metallic conductor (103), in the manner of the well-known salt-bridge experiment of Osterhout & Hill (133).

A complement to this experiment is that performed by Tasaki (153). Two nodes of a single nerve fiber are put in a narcotizing solution. A salt bridge is placed so as to conduct the current flowing from the node above those narcotized to the one below them, and a third arm of the bridge can also dip into the pool that bathes the narcotized nodes. When all three arms of the bridge are connected, an impulse originating above the pool cannot jump the inactive nodes; but when the pool is isolated from the other two

arms of the bridge, conduction takes place. This experiment is interpreted to mean that the current in the second case is sufficient to excite the distant node, but is insufficient when it is shared with intervening inactivated tissue.

The excitation of one fiber by the current of the activity of another has been described in crab nerve (109), but the impulse so developed arises only after a rather long latent period. Modifications of the excitability of one fiber, which are contemporaneous with the passage of an impulse in a contiguous fiber, have now also been described, again in the crab (114). For these measurements both fibers were placed on the same pair of recording electrodes and the excitability of the inactive fiber at the proximal recording lead was correlated temporally with the spike in the stimulated fiber. The excitability shows three phases, the first and the last being depressions and the intermediate one being an enhancement of excitability. The periods of decreased excitability have been ascribed to the electrotonic spread of the bioelectric current along the active fiber and back through the surrounding tissue, which also includes the fiber that is under test. At the testing electrode the current through this fiber would then be equivalent to an anodal polarization, hence the lowered excitability. During the period that the propagated activity is actually under the testing lead, the direction in which the current flows in the inactive fiber is reversed and the effect is a heightened excitability, such as would be produced by a cathodal polarization. Another application of the theory that the local bioelectric circuit is the transmitting agent of the propagated nerve impulse has been the demonstration (103) that the velocity with which the impulse in the nerve is propagated depends upon the electrical resistance of the external medium. In a medium of lower resistance the impulse travels faster than it does in a medium of high resistance. In one type of experiment with the giant fibers of the squid, Hodgkin was able to increase the velocity of the impulse by short-circuiting a stretch of the fiber with a metallic grid.

The accumulation of successful predictions and of explanations of experimental data have brought to the fore again the local circuit theory of the excitation and propagation of the nerve impulse, and the various forms of the chemical theory that have been suggested (45, 63) have lost relatively in strength. A blow to the chemical theory that the liberation of acetylcholine is the requisite

for excitation and propagation has been given by the failure to find acetylcholine in the dorsal roots (121). On the other hand, Lissák (120) has shown that adrenergic nerve fibers on stimulation produce epinephrine; while the cholinergic fibers, among which motor nerves are also included, develop acetylcholine. Proponents of the chemical theories may, therefore, claim with entire logicality that in the sensory nerves transmission is mediated by a third unknown substance. It may be recalled that von Muralt (131) in a preliminary account has reported that a substance, certainly not acetylcholine but otherwise of unknown nature and function, is liberated during the activity of mixed nerves.[5]

The mathematical formulations of the electrical theory have not yet succeeded in representing accurately all the experimental data. It has been shown that at least two of the versions, those of Hill (98) and of Rashevsky (138), are formally identical (132). Deductions made from recent experimental data which fail to be satisfied by these equations are concerned with the stimulation of nerve by alternating currents (113) and with the latent addition in the alpha excitability of muscle (22). However, so many features of the excitation and transmission of impulses have been described in either a qualitatively or a quantitatively successful manner that the validity of the electrical theory appears proven. Examples of the applications of the theory, in addition to those given here, will be found in the papers of Hill (98) and Rashevsky (138) and in the publications of H. A. Blair (21, 22). The keener insight into the physiological behavior that will be furnished by data of the type which has been reviewed here, as well as new information on the physical properties of excitable tissues, will undoubtedly lead to refinements of the mathematical formulations of the electrical theory

Recent data on the physical constants include studies on the optical properties of nerve (147), measurements of the resistance of vertebrate (46) and of invertebrate (43) nerve during rest, and of the impedance changes in resting (44) and active (42) giant nerve fibers of the squid and of the impedance of muscle under

[5] In this connection it is important to mention von Muralt's recent confirmation [Muralt, A. von, *Angew. Chem.*, **52**, 190 (1939)] of an older finding [Minz, B., *Compt. rend. soc. biol.*, **127**, 1251 (1938)] that thiamin is liberated during the activity of nerve. Kuhn *et al.* [Kuhn, R., Wieland, T., and Huebschmann, H., *Z. physiol. Chem.*, **259**, 48 (1939)] have synthesized Acetylthiamine and suggest that it may act as a chemical transmitter.

various conditions (91). In particular the finding that the capacitative impedance of the giant fibers changes very little, while the resistive component is profoundly modified during activity, is a contribution of the first magnitude. Another type of approach which promises success is the development of experiments by Tasaki (151, 152, 153) with single nerve fibers of the Japanese toad.

The proofs that have been presented for the electrical propagation of the nerve impulse along the fiber have recently been paralleled by evidence (112) that the nerve impulse can, when it reaches a muscle, set up in the latter effects which are definitely modifications of the excitable system (24, 119) of the muscle itself. In a partially curarized muscle fiber, the nerve impulse produces an enhanced excitability which long outlasts the nerve impulse and which decays at a rate characteristic of the alpha excitability of muscle.

There is still uncertainty as to whether the motor end-plate is an organ *sui generis*, or whether it is a region of the muscle fiber differentiated by reason of the intimate proximity of the nerve fiber (37, p. 49). In the resting single muscle fiber a very high potential difference has been observed between the surface of the end-plate and the surface of the muscle fiber (37). In lizard muscles this difference may amount to nearly 20 mv., but the sign of this potential is variable, the end-plate being positive to the muscle fiber in about two-thirds of the experiments. The same investigators have also recorded, both in the end-plate and in the muscle fiber, the potential changes that occur during activity. As has already been mentioned, localized responses have been recorded from the region of the end-plate in muscles of the frog (77) and the cat (53). Eccles & O'Connor have correlated with this potential a number of properties of the excitation process of the myoneural junction (54, 55). In partially curarized or fatigued preparations the localized responses may occur free from muscle action potentials, or the latter may appear upon the end-plate activity. The definition of their character will depend upon the conception of the nature of the end-plate. If the latter is conceived of as a separate organ, the end-plate potentials must be regarded as the full electrical response of the organ. Only if the end-plate is considered as a part of the muscle fiber can the potential be viewed as the sign of a localized prelude to propagated activity in the

manner that the local response of crab fibers must be viewed. In either case, the finding of the end-plate response would seem to indicate that primary action of curare is upon the transmission of the excitation from the end-plate to the muscle fiber. As a consequence of this view and because of the anti-curare action of physostigmine, it may be necessary to revise the concept that the motor nerves are cholinergic and to transfer this descriptive term to the end-plate.

The suggestion has recently been made (58) that in the frog the end-plate represents a synaptic discontinuity between the ventral root fibers and an intramuscular transmitting system, thus homologizing striated muscle to the smooth musculature. The motor nerve would be homologous to the preganglionic nerves, the end-plate to the peripheral ganglion cell, while the post-ganglionic fiber would be either very short or non-existent. Eichler's idea is based on further evidence (57) that the veratrine contracture of muscle is a continuous tetanus of the muscle fibers, which is accompanied by a discharge of action potentials (104). Eichler argues that the excitation causing the tetanus comes from the same direction as does the nerve impulse which initiated the first response, but since no secondary impulses are observed in the motor nerve, the activity must be in the end-plate and that the polarized structure of the latter, which prevents its activity from exciting the nerve antidromically, must be of the nature of a synapse.

A point of similarity between the behavior of the autonomic ganglia and the myoneural junction is the demonstration by Lanari & Rosenblueth (116) that the fourth and fifth stages of neuromuscular transmission of Rosenblueth & Luco (140) find their counterparts in the synaptic transmission through the superior cervical ganglion and through the parasympathetic system of the vagus to the heart. In the skeletal muscle preparation, in the nictitating membrane and in the pupil, as well as in the slowing of the heart rate, continued stimulation of the effector through the motor nerve or through the appropriate preganglionic fibers, after the first sequence of motor effects, causes a long continued depression—the fourth stage—which is then followed by a late rise, the fifth stage. Rosenblueth and his coworkers have shown that these events occur because of the intervention of the transitional element (the myoneural junction or the synapse) and have concluded that these events can be explained only on the basis of a chemical

theory of transmission. Other explanations, however, also seem possible. For example, Lanari & Rosenblueth state (116, p. 355) that "even a slight interference with the blood supply of the superior cervical ganglion prevents the appearance of the fifth stage." This may indicate that the fourth and fifth stages are modifications of the excitability produced by metabolic products. Accordingly, the fourth stage would be attributable to a depression of excitability by the accumulation of metabolites, while the fifth stage would represent the removal of these after diffusion into the circulation. It is characteristic of the state of our lack of knowledge of many essential data that the same type of explanation may be given an entirely different cast. The fourth stage might represent a depletion of some metabolite and the fifth stage the gradual restoration through its mobilization from other regions of the body. Furthermore, the existence in nerve of the more subtle changes in the excitability, which last for relatively long periods of time, suggests the possibility that similar effects may also exist at the synapse, in the myoneural junction, and in the muscle.

Evidence which began with Bremer's demonstration of long-lasting latent addition (30) indicates that long-continued changes of the excitability may take place in the myoneural junction. Thus, partial curarization discloses in the mammalian nerve-muscle preparation (34) a period lasting fifty milliseconds, during which two ineffective stimuli may be summated, and which is then followed by a depression of excitability lasting about one second. Neuromuscular "fatigue" can take place at the curarized myoneural junction and, therefore, without the participation of the muscle in the activity (128).

Other experiments show that subsequently to a tetanus delivered through a motor nerve to a muscle of the cat (35) and of the fowl (36) the excitability of the muscle is heightened. The effects in the cat have been compared with those produced by the close arterial injection of potassium chloride and the role of the mobilization of the potassium ion has been stressed. The role of the potassium ion in excitation is also dealt with in two new experiments (37, 38). Brown & MacIntosh (37) find that close application of potassium chloride stimulates nerve fibers directly. They explain the failure of potassium chloride injections to stimulate a nicotinized ganglion as attributable to a block of the synaptic transmission of the preganglionic discharge that is evoked by the

potassium chloride. The ability of acetylcholine to excite the poisoned ganglion thus indicates a differentiation in the sites of action of the two substances. A different localization obtains in the muscle end-plate. Buchthal & Lindhard (38) find that the end-plate is directly excitable by potassium chloride, and is excitable even when a previous application of acetylcholine has rendered the end-plate irresponsive to further additions of the drug or to the nerve impulse.

The action potential of striated muscle.—The recording of the complete action potential of striated muscle is accompanied by difficulties all of which are probably not yet solved. Among the complications that may play their parts are: (1) spurious potentials produced by the movement of the muscle upon the electrode, (2) the difficulty of interpreting records led from a conductor of large volume, (3) the probability that the responses of the muscle fibers are to some degree asynchronous, (4) the modifications that may be expected to occur rapidly in an organ which has a relatively high rate of metabolic activity. The significance of still another factor cannot be evaluated at present, but its implications should be pointed out. In the retrolingual membrane of the frog, the single muscle fibers often branch near their terminations. Light pressure applied to one-half of the undivided fiber blocks the contraction of the branch on the compressed side (150). This finding may indicate that the transmission of the excitation in the muscle fiber follows along intramuscular fibrillar pathways, and in any case the transmission appears to be effective only at close range, since it is unable to spread across the entire fiber below the point at which the pressure was applied.

In accordance with the complexity of the problem, it is not surprising that the action potential of the striated muscles of the frog (143) presents several different forms and that the occurrence of any of these cannot be predicted from a knowledge of the experimental conditions. A spike lasting two to four milliseconds is succeeded by negative and positive potentials which may vary as to their relative duration and amounts. In the sartorius muscle the negative potential ends at the crest of the muscle twitch, and in the gastrocnemius it continues throughout the contraction. Schaefer & Schölmerich (144) have recently investigated the changes produced in the action potential by poisoning the muscle with bromoacetic acid to eliminate the aerobic glycolysis of the normal metabolism. The effect of the poisoning is to remove, when it has

existed before, the long-lasting negative potential that succeeds the spike.

The potentials of smooth muscle.—Smooth muscle presents even greater difficulties to the electrophysiologist than does striated muscle. The conditions that complicate the recording of the action potential in striated muscle likewise hold for work with smooth muscle. In addition there are other factors: (1) the extremely small size of the fibers; (2) the absence of well defined innervation of all the muscle fibers; (3) the extreme susceptibility of smooth muscle to the modifying effects of hormones, neurohumors, drugs and of seasonal and environmental variations; and (4) the frequent occurrence of spontaneous rhythmic activity. Accordingly, a number of divergent interpretations have been given of the electrical response and also of the electrical excitability of smooth muscle; these have been considered by Bozler (28). Space permits only the discussion of the recent very careful and well controlled experiments of Bozler (26, 27, 29) which have served to throw new light upon the problem. According to these experiments, it appears that smooth muscle has a syncytial structure. The muscle fibers are electrically excitable, present a definite strength-duration curve and a definite absolutely refractory period. They are able to propagate the contraction and produce a spike response. Tetanization of the muscles is possible when the absolutely refractory period does not exceed the duration of the mechanical response. An interesting fact is that in the uterus of the anoestral cat electrical excitation does not occur, while in the anoestral guinea pig propagation of the impulse is not found. In both cases, however, these deficiencies are removed by the administration of theelin. Spikes also occur in the bursts of spontaneous rhythmic activity, and gradation in the size of the rhythmic activity is evidenced by variations in the number or the frequency of the spikes. Variations in the sizes of the spikes of spontaneous activity also occur and presumably are attributable to the incomplete activation of the syncytium. There is, accordingly, no reason to consider the electrical activity of smooth muscle as representing a physiological system very different in nature from the electrical activity known for either nerve or muscle. Indeed, Bozler (27) states that in the ureters of most of the species of animals that he studied the electrical response is a fused one of long duration, similar to that found in another syncytial system, the heart.

Potentials of nerve cells.—Since nerve cells are arranged in

masses, or in layers among other types of structures, or among inactive cells, the problem of interpreting the potentials resulting from their activity assumes all the complexity of the interpretation of records of potentials of unknown form produced in indefinite regions of volume conductors. A discussion of the electrical problems involved, as well as other references, will be found in the paper of Lorente de Nó (126). To this purely physical difficulty is added another, that of the anatomical complexity of the functional interconnections of a cell with its neighbors and with more distant groups of elements (124).

The methods that have been used to study the potentials resulting from the activity of the nervous system may be grouped into four general classes: (1) recording by placement of large electrodes upon the surface of the region involved in the activity (13, 73); (2) exploration of the active region with microelectrodes (15, 139); (3) leading from the dorsal (10) or the ventral roots (57) the potentials developed in them as a result of central activity and (4) study of the physiological effects of one or more bursts of activity. To this type of experimental approach belong the investigations regarding the temporal course of the response, either in the nervous system itself or in the effectors, and those on the modifications of the excitability which activity, a stimulus, or experimental procedures produce in the nervous system (126).

The magnitude of the problems involved in the study of the potentials produced by nerve cells has led to the development of a new discipline and of a vast literature, which is separately reviewed in this volume. Here it is proposed to deal only with those aspects of the problem where correlations have been made between the potentials of groups of nerve cells and of peripheral nerves.

Ganglionic potentials.—It is relatively easy to get at the potentials of the nerve cells found in the ganglia of the mammalian autonomic system (32, 51). No detailed description of these will be given, because the data were reviewed in the previous volume (33). It is important to note, however, that the potentials recorded from the superior cervical ganglion (51) and from the inferior mesenteric ganglion (121) are similar to the potentials recorded from the postganglionic C fibers (90). An extensive comparison of the ganglionic potentials with those found in nerve has recently been made by Lloyd (122). The potentials recorded from the ciliary ganglion (156) appear to be like those recorded from B fibers

(89). Although there exist no potential data on the type of fiber in the postganglionic fibers in the ciliary nerves, it is known (40) that the fibers are small and myelinated; and it thus appears likely that in this parasympathetic ganglion the cells have axons and potentials of the B type.

The relative magnitudes of the components of the action potential may differ (51) from those of the axons. However, it is a difficult matter to stimulate all the cells of a ganglion simultaneously and thus, by eliminating dispersion, to get a correct measure of the size of the after-potential in terms of the height of the undispersed spike, as is the practice in nerve. Purely physical conditions, which may affect their magnitudes as well as physiological modifications of the labile after-potentials, make it advisable to suspend judgment on this matter at the present time.

Other properties of the cell are also similar to those of their axons. The refractory period and the period of subliminal summation are the same in the cells and in the axons (51, 89, 90). The recovery of excitability of the cells (51) may under certain conditions parallel temporally the course of recovery of the axons (90).

The after-potentials which in the stellate ganglion follow repetitive activity have been recorded by Bronk and his associates (32). As in nerve, the excitability parallels the after-potentials, and the changes that occur in it during the course of the after-potentials control the discharge of the neurons, whether this arises as a result of the spontaneous variations of the threshold or in response to changes in the chemical environment (acetylcholine, calcium, etc.).

It, therefore, appears possible to generalize that the cells of autonomic ganglia develop potentials which in their form, time course and in their correlations with other properties are identical with the potentials developed in their axons.

Potentials of the central nervous system.—It is not so easy to find correlations as direct as the above between the potentials developed in the central nervous system and those in peripheral nerves. Two factors complicate especially the interpretation of the potentials of the central nervous system. The asynchronous long continued type of discharge, which is characteristically the response of the central nervous system to stimulation, is attributable chiefly to the possibilities which exist for reverberation (124) in the central nervous system and which are due to the enormous com-

plexity of the interconnections. This asynchronism in the response makes temporal correlations difficult. The second difficulty is concerned with identifying the sign of the potentials that are recorded. In a volume conductor which has embedded within it the sources of the recorded voltages, the sign of the potential signifies nothing more than that the current is flowing past the electrodes in a certain direction. The sign of the potential may accordingly be reversed as the exploring electrode is moved. In relatively simple situations (139 and a paper in press) it is possible to show this reversal and to utilize it for important deductions, but in the more complex situations, which are the rule, certain identification of the sign is impossible.

Since in most cases neither the time relations nor the sign of the potential can be reduced to their simplest elements, only scattered correlations are possible between the electrical properties of the central nervous system and those of peripheral nerve. Various regions of the central nervous system have yielded data on one or more such points as these, and an attempt will be made to gather these without restriction as to the anatomical site of the experimental material.

Spikes.—The cord potential, which consists of a negativity lasting 15 to 20 msec. and of a positivity of about 100 msec. or more duration, certainly represents a complex recorded from the activity of many asynchronous elements. Much of the early potential of the spinal cord electrogram is made up of contributions from spikes (Renshaw, unpublished), and spikes are also known to be produced elsewhere in the central nervous system (15, 48, 126, 139). These spikes have durations that approximate those of peripheral A fibers. In keeping with the short duration of the spike is the short duration of the absolutely refractory period, which at the synapse is of the order of 0.5 msec. (126). The period of the classical subliminal summation is also short in the central nervous system (about 0.4 msec.), as it is in peripheral nerve.

The potentials of motoneurons.—A valuable method of studying the potentials of the motoneurons was developed by Eccles & Pritchard (56). The neurons are excited antidromically and the potentials are recorded electrotonically by leads placed on the motor roots. An interesting question still remains unanswered as to why the intramedullary potential, which is here pitted against the potential of the nerve at the second lead, outweighs the latter.

That it does do so is unquestionable, and the time relations of the potential (cf. Gasser, 70) are identical with those found in peripheral A fibers. There is a negativity which follows the spike and which lasts for about 15 msec., and a positive potential which continues on for 50 to 60 msec. more.

Recording the potentials of the oculomotor neurons with needle electrodes placed in the nucleus, Lorente de Nó (126) has found that after either antidromic or synaptic activation, the spike is followed by a negativity for an interval varying from 15 to 20 msec. (126, Fig. 15–2, 3) to 30 msec. or more (126, p. 435). The sign of the subsequent potential, if any existed, was not traced.

A disturbing element, which makes it hazardous to identify the potentials of elements of the central nervous system with those of peripheral nerves, is the fact that no supernormality has been observed in the former.[6] Recovery from the subnormality following activity takes the form of a continuous rise out of profound subnormality, which lasts as long as does the positive potential in all parts of the central nervous system thus far studied (66, 70, 106, 126). It is important to note that the antidromically conditioned motoneurons of the oculomotor nucleus (127) are subnormal to synaptic excitation at a time when the soma of the cells is supernormal to direct electrical stimulation. Furthermore, we may recall the finding made by Eccles (51) that the antidromically conditioned cells of the superior cervical ganglion recover along a subnormal course throughout, while conditioning synaptic stimulation leads to a recovery curve which passes through supernormality and which has a form identical with the recovery curve of the peripheral C fibers (90). These two observations indicate the complexity of the problem that faces an attempt to homologize the negative potential of the central nervous system with the negative after-potential of nerve. There are two possibilities which may be summarized by quoting from Gasser (70, p. 368): "One may question whether there is any negative after-potential included in the recorded negativity. If there is, there must be an additional factor controlling excitability which has not yet been resolved."

No such difficulty opposes the identification of the positive potential. Gasser (70, p. 368) states: "The positive potential of the

[6] Eccles & Pritchard in their preliminary account (56) report a low threshold during the negativity. An evaluation of this result must await the full publication of their data.

motor neurons not only has the duration of the positive after-potential in motor axons, but it is attended by the expected subnormality. There is indeed no reason for not calling it the positive after-potential of the neurons."

The response of the motor neurons—a spike, then negativity lasting for about 15 to 20 msec., followed by a positive after-potential—is in its pattern so strikingly like that of the axons that it seems fruitful to follow the second suggestion made by Gasser and to explore the possibility that additional factors affect the excitability of the motoneurons and disguise or abolish supernormality.

One such possible factor will be described here, since it involves the application of data that have been obtained on peripheral nerves and that are in accord with the theory of the electrical transmission of the nerve impulse. This application is based on the evidence of Katz & Schmitt (114) that in an inactive fiber there is set up a period of depressed excitability through the anodal polarization which is produced by the current flowing in it as a result of the activity of a contiguous fiber.

During the period of recorded negativity following antidromic activation of the nerve cells a current must be flowing into them from the less negative axons, and a proportion of the interneuronal dendrites surrounding the cells will be properly oriented to become anodally polarized. If in some of these the polarization should reach proportions sufficient to block the conduction of the testing impulse into the synaptic terminations, the experimental measurements would indicate that a stronger synaptic stimulus is necessary. The data would then be interpreted as a subnormality of the synapse, even though the cells may be (and are, 127) supernormal to direct electrical stimulation. The curve of synaptic recovery would then take on the form of continuous subnormality, because the period of the block due to this electrotonic presynaptic effect would merge into the period which is marked by the positive after-potential and during which the excitability of the cell is subnormal.

On the basis that a phenomenon such as this may be a modifying factor in the very complex anatomical physiological and electrical conditions which exist in the central nervous system, an identification of the recorded negativity with a negative after-potential is very tempting. Further experimental information must be looked to for a critical answer to this question.

A new step in the direction of experiments such as these has

been taken in an important paper by Dusser de Barenne & McCulloch (49), in which are studied the modifications undergone by the excitability of the motor cortex of the monkey when various experimental procedures are applied. Correlations have been made by these authors of the conditions that promote facilitation and those that aid the extinction of motor responses produced by cortical stimulation. The factors which are of immediate interest in the present discussion and which induce facilitation are: (1) "negative voltage drift associated with decrease of threshold in neurons previously involved," and (2) "probably increase of pH (alkaline shift) . . . " Changes in the opposite directions of a positive voltage drift and of an acid shift are factors for extinction.

An interpretation in terms of the electrical theory of the mechanism of synaptic transmission and of the problems of synaptic excitability has been given by Lorente de Nó (126). It correlates the phenomena occurring in the central nervous system with those which take place in peripheral nerve, especially with those which are evidenced in the latter in the region of a block produced by cocaine. This interpretation affirms the current concept that "detonator action" (52, 126) when it activates is similar to the electrical excitation of an inactive region (20, 102, 103, 153), and when it is below threshold produces a short period of enhanced excitability (19, 100, 101, 126, 153). The negative potential that follows the spike in the central nervous system, Lorente de Nó (126) homologizes with a residual negativity which he has observed in the blocked nerve. He points out (126, p. 453), that such "residual negativity at synaptic knobs could cause (a) second phase of summation" and thus be responsible for the "central excitatory state," which Eccles (52) has postulated as the mediator of a lowered threshold that is one cause of facilitation. It is worth while remembering that in some cases (126, Fig. 9) facilitation may last for only 5 to 15 msec., while in others, presumably because they involve more synapses and structures, long-continued facilitation is the rule (126, Fig. 8). The lowered excitability of the cell to synaptic stimulation during this "residual negativity" left behind by previous activation Lorente de Nó explains as attributable to the acquisition by the cell of a higher threshold in the period during which the soma is negative to the axon. This condition is likewise in analogy with a correlation which he finds exists between the threshold gradient and the potential gradient in a regional block of a nerve.

The recent experimental contributions to the chemical theory have been describe in the first volume (33). During the past year there has appeared the full discussion by MacIntosh (128a) of the objection which he has raised to the conclusion of Lorente de Nó (124a) that the production of acetylcholine is not necessarily correlated with synaptic transmission in the superior cervical ganglion. The reader is also referred to a recent summary of the evidence for chemical transmission by Forbes (63).[7]

Potentials in the interneurons.[8]—An impulse delivered into the interneurons sets up spike activity and a slow potential which lasts for 15 to 20 msec. when the potentials of the interneurons are recorded by a microelectrode (126). During this time there is also heightened activity among the interneurons. This phase of slow potential, the sign of which may be either negative or positive, and of heightened activity is succeeded by a potential of opposite sign lasting for 35 to 40 msec., during which there is a silent period (126, Fig. 16–6). It is needless to stress the resemblance that exists in the records cited to those from a nerve in which spontaneous activity is taking place. However, in the more complex records of the spinal cord (105, 106) the recovery of the interneurons is similar to that of the motoneurons and proceeds along a continuously rising curve without the development of supernormal excitability.

Potentials of the dorsal roots.—As these potentials have been discussed in two reviews published in the previous volume (33, 52), only new work will be considered here. Bonnet & Bremer (25) report that in the frog there is a correlation between the amount of reflex activity and the size of the negative component in the dorsal root potential of a conditioning volley. Although there exists at present no comparison between the cord potentials of the frog and the mammal, these authors believe that their data on the dorsal roots constitute a parallel to and a confirmation of the correlation which exists between the cord potential and the inhibition of reflex activity in the mammal.

The origin and function of the reflex discharge in the dorsal roots (154) still remain unknown. Barron & Matthews (11) find that the discharge is much increased by cooling the cord a few degrees; and they believe (12) "that one-way conduction at the

[7] See also the statement of the evidence as made by Dale, H., *Science*, N.S., **90**, 393 (1939).

[8] The term "interneuron" is used in agreement with Lorente de Nó (126) as the abbreviation for internuncial neuron, as suggested by Gerard.

synapse is so delicately balanced that even a fall of temperature of a few degrees causes a partial failure." Toennies, however, has shown (155) that the reflex discharge is present even at 40° C.

Full discussion of many other significant correlations of phenomena in the central nervous system is given in the "Symposium on the Synapse" by Gasser (70), Erlanger (60), Bronk (32), Lorente de Nó (126) and Forbes (63), to which many scattered references have been made in the foregoing text.

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THE CENTRAL NERVOUS SYSTEM[1]

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The following summary will deal with the major advances in the physiology of the nervous system since January, 1938, when I had occasion to give a detailed review in a general monograph. Since the sensory systems are being dealt with in the present volume by Marquis, the survey will be limited to the motor systems of the suprasegmental levels (for the spinal cord, see Eccles's review, 1939). The special field of electrophysiology of the cerebral cortex, insofar as this has been advanced by the new technique of electro-encephalographic study, will not be treated since this has just been covered by Davis (1939). The principal advances in knowledge of nervous functions fall into five categories in accordance with levels of function: the medulla oblongata, cerebellum, hypothalamus, striate bodies, and the cerebral cortex. They will be discussed in this order, and will be followed by an account of the general properties of central nervous tissue.

The Medulla Oblongata and Respiratory Movements

The most notable development in the physiology of the medulla oblongata especially of its large and ill-defined reticular formation, has been the positive localization of the several respiratory centers by Pitts, Magoun & Ranson (1), coupled with their

[1] Perhaps the most important event of this year in the physiology of the nervous system is the publication in November 1939, of the *Selected writings of Sir Charles Sherrington* issued under the editorship of Derek Denny-Brown (London, Hamish Hamilton; New York, Paul B. Hoeber). It combines the old with the new. The irresistible logic illustrated in the sequence of Sherrington's scientific papers, beginning with the distribution first of the motor and then the sensory nerve roots, later with the sensory nerves to muscles, the spinal animal, reciprocal innervation, postural reflexes, the motor area of the cerebral cortex, and finally with the nature of excitation and inhibition—all these when brought together in Sherrington's original sequence form a document that becomes a milestone in the history of contemporary physiology. Any review of the present state of knowledge of the nervous system must take up threads from this fundamental document.

The first two volumes of the newly established *Journal of Neurophysiology*, which began to appear in January 1938, give an interesting indication of trends in this field.

analysis of the interrelation of these centers (2). Using the Horsley-Clarke stereotaxic instrument for stimulation, they have found a well-defined inspiratory area lying in the ventral reticular formation of the cat's medulla oblongata lying immediately over the inferior olive. When this region is stimulated electrically, the chest and diaphragm remain in fixed maximal inspiration, rhythmic breathing is abolished, and death may occur if the stimulation is continued.

An expiratory area was similarly delimited and was found to lie "dorsal to, slightly cephalic to, and cupped over the cephalic end of the inspiratory reticular formation." The expiratory movement evoked by stimulating this area is somewhat less intense than the inspiration evoked from the inspiratory area, but it involves both thorax and diaphragm and in some instances is maximal. If stimulation persists, a maximal expiratory posture may be maintained for two to three minutes, but death does not supervene, since inspiration gradually breaks through. The respiratory movements observed in these studies were well integrated respiratory acts involving simultaneously thoracic and diaphragmatic musculature and hence cannot be due to stimulation of efferent or afferent fiber tracts, but rather to a focus of neuronal integration. Reactions were independent of the anesthetics used, and they could also be obtained in unanesthetized animals having surgically implanted electrodes. Caudal to these foci, expiratory and inspiratory hyperactivity could be obtained in the presence of superimposed rhythmic respiration. The latter effects were interpreted as due to stimulation of descending tracts. In passing one should note that the precise localization of the inspiratory and expiratory centers given by Pitts, Magoun & Ranson (1) coincides with the general localization of the corresponding center in man given by Finley (1) in his two cases of primary respiratory failure from the medullary lesions.

Respiration is also influenced from supramedullary levels. Thus, Magoun finds that the well known inhibitory effect on respiratory movements resulting from hypothalamic stimulation is considerably depressed when the hypothalamus is stimulated some weeks after removal of the cerebral cortex. This suggests that the normal response is due to activation of corticofugal fibers which pass from the cortex through the hypothalamic area.

New light upon the part of the cerebral cortex, concerned in regulation of respiratory movements has recently come from the experiments of Bailey &

Bremer, who found that, when the central end of the vagus nerve was stimulated, conspicuous changes occurred in the electrocorticogram of the orbital surface of the frontal lobe in cats and in no other region. More recently, Bailey & Sweet (unpublished) find that electrical stimulation of the orbital part of the frontal lobe causes inhibition of respiratory movements. It had formerly been thought (see Bucy & Case, Walker & Green, Smith) that area F.6*b* (Fig. 1) on the lateral surface of the frontal lobe also inhibited respiration. Bailey believes that effects when obtained from this area are probably due to spread of current along the moist orbital bone to the orbital surface of the frontal lobes. Acceleratory effects on respiration may be obtained from points on the lateral surface of the frontal lobe—in the monkey from the anterior part of area L.6 (Fig. 1) near the midline (Smith).

Another study on the medulla is that of Wang, who finds that local application of pituitrin, pitressin, histamine, and acetylcholine to the floor of the fourth ventricle in cats under pentobarbitol anesthesia causes a small depressor response. With acetylcholine, however, there may also occur a delayed pressor response following initial depression.

The Cerebellum

The usefulness of the Larsell-Dow subdivision of the cerebellum into the functional units of, (i) the flocculonodular lobe and (ii) the corpus cerebelli has been richly vindicated by Holmes, by Bailey, Buchanan & Bucy and others in their recent analyses of cerebellar syndromes in man. The flocculonodular lobe, lying for the most part in the roof of the fourth ventricle and separated from the corpus cerebelli by the fissura posterolateralis, is the only part of the cerebellum which both receives and sends fibers directly to the vestibular nuclei [Dow, (1)]. Isolated lesions of this area give rise to disturbed equilibration without causing any of the more conspicuous signs of cerebellar deficit. The finger-to-nose test is performed perfectly, there is no terminal tremor in animals, but both man and ape, after a lesion of the nodulus, walk with a swaying gait and a broad base.

The corpus cerebelli is made up of two large divisions, one neocerebellar, i.e., the cerebellar hemispheres, and the other paleocerebellar, i.e., the anterior lobe. The neocerebellum is concerned with the integration of volitional reactions. Lesions restricted to the cerebellar hemisphere cause disturbances in the rate, range, force, and direction of volitional acts, leading to terminal intention tremors and other discontinuities of movement. These disturb-

ances are all accentuated when the lesion involves the underlying dentate nuclei, a correlation worked out by Botterell & Fulton in monkeys, and earlier in man by Holmes.

Fresh information concerning the anterior lobe has come through the recent studies of Gervase Conner (unpublished). He finds that isolated lesions of the culmen, simplex, and lingula cause disturbances restricted to the postural sphere. It has long been known that stimulation of this area caused inhibition of decerebrate rigidity and of other resting postures, but prior to Conner's studies, it had not been fully established in the higher animals that increased tendon and stretch reflexes with continuous spasticity accompanied by lengthening and shortening reactions, clonus, etc., were caused by isolated lesions of the anterior lobe (*see* Fulton & Connor.) Similar phenomena have been observed following lesions of the anterior lobe in the pigeon, and it is now evident that spinal stretch reflexes in higher animals are also specifically released by lesions of this area.

It therefore follows that in the somatic sphere the cerebellum exhibits functional localization of mechanisms essential for: (i) equilibration (the flocculonodular lobe), (ii) skilled movements (the neocerebellar hemispheres), and (iii) postural reflexes (the anterior lobe). In keeping with this tripartite functional division Dow (4) finds that cerebellar action potentials induced by stimulating the eighth nerve are restricted to the flocculonodular lobe those from dorsal spinal nerve roots, to the anterior lobe, and those from motor cortex and pons, to the neocerebellar hemispheres.

The cerebellum also influences autonomic reactions. The recent studies of Moruzzi (1, 3) indicate that weak stimulation of the anterior lobe may cause a fall of the systolic pressure, especially when the latter has been abnormally elevated. Carotid sinus reflexes which develop following strong stimulation of any pain nerve of the body may likewise be inhibited from the anterior lobe. Like the cerebral cortex, the cerebellum has thus an overlapping representation in the somatic and autonomic spheres. To quote Moruzzi (2, p. 536):

Le champ d'action du cervelet n'est donc pas limité à la musculature squelettique: il englobe des activités fondamentales de la vie végétative qui sont contrôlées comme le tonus postural, par les centres de corrélation du tegmentum bulbo-protubérentiel.

Voronine & Zimkine (1935) have also reported that anterior lobe stimulation causes inhibition of peristaltic activity of the gut.

The Hypothalamus

Detailed reviews of the physiology of the hypothalamus have recently appeared in the *Ergebnisse der Physiologie* [Ranson & Magoun, 1939] and in greater detail in the 1940 volume of the *Association for Research in Nervous and Mental Disease*, which devoted its recent meeting (December 20 to 21, 1939) to the hypothalamus. The most important developments of the last two years have related to functional localization of the hypothalamus, especially in relation to heat regulation and water metabolism. There are also two new anatomical disclosures which have an immediate bearing upon functional activity of the hypothalamus.

Blood supply.—The work of Finley and of Craigie indicates that the supraoptic and paraventricular nuclei are with the locus caeruleus the most highly vascularized areas of the entire brain, having a capillary bed at least six times more extensive per square millimetre of tissue than that of the gray matter of the motor cortex. This suggests, along with other comparative anatomical evidence, that these highly vascularized areas surround neurons which are specifically responsive to changes occurring in the blood, be they chemical or thermal.

The supraopticohypophyseal tract.—Within the past two years evidence has accumulated which clearly establishes the existence of a large tract, passing from the hypothalamus to the pituitary, through the pituitary stalk. Rasmussen (1, 2) estimates in man that there are approximately 100,000 fibers in the stalk; in the monkey 50,000; in the rat 10,000. When the stalk is severed near to the pituitary (i.e., just above the diaphragma sella) the cells of the supraoptic nuclei undergo retrograde degeneration and disappear; in monkey's supraoptic nuclei cells diminished from 34,000 to 9,000. When the stalk was severed near to the hypothalamus, the cells diminished in number from 34,000 to 6,000. Brooks & Gersh have traced certain of these fibers to specific cells in the posterior lobe complex, and they have described the character of their endings. Hair & Brooks have traced a few fibers also to cells in the anterior lobe. It is probable that the tuber nuclei as well as the supraoptic, contribute to the nerve pathway to the pituitary. No one has determined whether this outflow is sympathetic or parasympathetic in its affinity, although Pickford has given evidence that the posterior lobe complex appears to be cholinergically activated. This would favor the assumption, well substantiated on other grounds, that the supraoptic is a parasympathetic nucleus.

Heat regulation.—Writing in June, 1932, Keller & Hare stated, "the chief central mechanism controlling heat production is located in the hypothalamus, and that extirpation of this region releases the heat loss mechanism, located elsewhere, from coordi-

nated control."[2] The most important recent studies in this field are those of Ranson and his pupils.[3] They have found by local heating (high frequency currents passing between two implanted electrodes) that in cats the mechanisms of heat loss, especially panting, are activated when the temperature of the anterior hypothalamic area is raised. The region included a cube about 8 sq. mm. in extent lying in the midline immediately above the optic chiasm and extending rostrally into the preoptic area and no other part of the forebrain. The responses could not be obtained when the electrodes were applied more than 4 mm. from the midline. The generalized panting began within about thirty to sixty seconds after the application of the heating current and was accompanied by sweating of the pads of the feet and by some vasodilatation. Rectal temperatures always fell several degrees centigrade as a result of the panting and sweating, but the extent of the fall is not reported.

Since the mechanisms of heat production are activated by the posterior hypothalamus (Keller & Hare; Bazett, Alpers & Erb), it follows that they are primarily governed by adrenergically (sympathetic) innervated structures coupled with the somatically controlled shivering reflex; the mechanisms of heat loss, on the other hand, are primarily governed by cholinergic (parasympathetic) mechanisms including sweating, vasodilatation, etc., coupled with the somatic reaction of panting. The function of maintaining body temperature is thus a highly integrated reaction involving both divisions of the autonomic system as well as important somatic reactions.

Intimately linked with the mechanisms of temperature regulation is the control of water metabolism and thyroid secretion.

Water metabolism.—Gersh has identified the cells of the posterior lobe and median eminence which are responsible for elaborating the antidiuretic substance essential for water conservation. These cells are so intimately dependent upon their nerve supply

[2] Dr. Keller's studies on this subject began in 1929 at Yale University and a preliminary communication on heat regulation in brain stem preparations was made April 1930 [Keller (2)], but detailed description of this historically important investigation did not appear until November 1938 [Keller (1)]. Although Isenschmid & Schnitzler had suggested much earlier that the hypothalamus is concerned in heat regulation, their work was overlooked and Keller must be given credit for having first clearly proved that the hypothalamus is essential for temperature regulation.

[3] *See* Magoun, Harrison, Brobeck & Ranson.

from the supraoptic nucleus that when the latter is destroyed, not only the fibers in the stalk but also the cells, which they innervate, degenerate (Fisher *et al.*). When this occurs, the condition known clinically as "diabetes insipidus" supervenes. Similarly, when the secreting cells are themselves destroyed without direct injury to the hypothalamus, diabetes insipidus ensues. If only the posterior lobe is removed the homologous cells in the pituitary stalk and median eminence hypertrophy and provide sufficient anti-diuretic substance to prevent undue water loss through the kidneys. In addition to having solved the problem of the mechanism of diabetes insipidus, the work of Gersh also indicates that water conservation is under the direct control of the hypothalamic area. It would seem scarcely an accident that the same region of the brain that controls the kidney likewise is essential for regulating body temperature.

Hypothalamic control of the thyroid.—Scarcely less significant from the point of view of heat regulation are the recent studies of Uotila (1, 2), the distinguished young Finn, who finds that the thyrotrophic hormone of the anterior lobe, which is normally released when a rat is subjected to a cold atmosphere, fails to be released if the pituitary stalk has been previously sectioned (without damage either to the anterior lobe itself or to the hypothalamus). In a group of rats with stalks sectioned, Uotila found that, whereas there was sufficient activation of the thyroid to prevent its atrophy at room temperature, the thyroid failed to show the cold reaction (follicular hypertrophy) when the animals were placed for several days in a cold environment. The body temperature of the latter group of animals fell slowly, and the majority ultimately died when their body temperatures were 15° to 20° below normal. Again it is scarcely surprising that the same region of the brain responsible for heat regulation is also concerned in regulating thyroid secretion.

For other phases of recent work on the hypothalamus, the reader is directed to the monograph of Clark, Beattie, Riddoch & Dott, the review of Magoun & Ranson and the 1940 volume of the *Research Publications of the Association for Research in Nervous and Mental Disease.*

The Striate Bodies

There is little new to report concerning the functions of the motor systems originating in the corpus striatum. Rioch & Bren-

ner's important paper on electrical stimulation of the striate bodies some weeks after the cerebral hemispheres had been removed, led them to the postulate that "in the mammal the striatum does not have an autonomous function, but acts only in conjunction with other systems." A few isolated reactions, however, were found in their chronic preparations, such as eye movements (conjugate deviation to the lateral side); occasionally also there were stereotyped movements of the extremity similar to those which sometimes occur spontaneously in these preparations. More often such stimulation precipitated a rage reaction, due possibly to activation of the hypothalamus. From the tuberculum olfactorium and pyriform lobes, they obtained chop-licking, salivation, swallowing, sniffing, etc., which again were similar to the normal patterns of response of the decorticate animal when presented with a strong olfactory stimulus.

Recent studies of Dusser de Barenne & McCulloch (2, 3) likewise suggest a close functional interconnection between the striatum and the cortex. They report in the monkey that local strychninization of area 4-s (Fig. 1)—the "strip" region of Hines—leads to activation of neurons in the caudate nucleus which in turn activate the thalamus, and, through thalamocortical projections, area 4 is finally affected, thus establishing a functional one-way system involving in turn: (i) strip region, (ii) caudate nucleus, (iii) thalamus, (iv) motor area, i.e., area 4. They give the following interpretation,

> The experiments reported, therefore, constitute a demonstration by physiological means that the striatum, more particularly the caudate nucleus, does not function independently of the cerebral cortex. On the contrary, it is shown here: (i) that the specific areas (A.4-s and L.4-s) of the sensory motor cortex directly influence, excite and activate the caudate nucleus, (ii) that the activity of this subcortical structure influences, or "brakes," albeit indirectly, via the optic thalamus, the the activity of other equally specific areas (A.4 and L.4) of the same sensorimotor cortex. (See Fig. 1.)

The work of Mettler, Ades, Lipman & Culler also points to the close functional interrelationship between cerebral cortex and basal ganglia. They find that stimulation of the caudate nucleus, putamen, or claustrum inhibits movements induced by cortical stimulation, the effect being most conspicuous when the basal ganglia are stimulated on the same side as the activated cortex. Excitation of the globus pallidus, on the other hand, is said "to

impart a factor of 'plastic tonus' to cortically induced movements." These authors emphasize that the failure of previous investigators to demonstrate excitability of the striatum arises from the fact that no one in the past has stimulated the striate bodies while a cortically induced movement was already in progress. This new approach to an old problem is obviously one of the most promising so far recorded in this difficult field.

Specific lesions of the striatum have been reported by Richter & Hines who believe that involvement of the head of the caudate nucleus in monkeys is primarily responsible for the states of motor hyperactivity which follow bilateral lesions of the frontal lobes (see below). Brown finds in monkeys that tremors develop following large bilateral lesions of the putamen or after smaller lesions of both pallida; the tremor is transient, but may reappear even after a unilateral striatal lesion, if areas 6 and 8 of the cerebral cortex are simultaneously ablated. Brown's studies thus further substantiate the existence of a close functional interrelation between cortex and striatum.

In an unpublished study with Dr. Aring it was found, both in monkeys and chimpanzees, that hemidecortication causes a greater degree of spasticity in the affected extremity when the corpus striatum is allowed to remain intact than when it is removed along with the cerebral hemisphere. According to Verhaart, at whose suggestion this work was undertaken, flaccid hemipareses of vascular origin show lesions that involve, not only the internal capsule, but also deeper nuclei including the thalamus. It would thus appear that the integrity of the basal ganglia, and possibly the thalamus, is essential in primates for the maintenance of high degrees of spasticity following removal of the cerebral cortex, or after a capsular hemiplegia.

Cerebral Cortex

The more important recent studies on the motor function of the cerebral cortex have employed the older techniques of stimulation and ablation; knowledge has also been advanced through analysis of regional electrocorticograms and the influence upon these of stimulating, by strychnine or electrical excitation, of other cytoarchitectural areas [Dusser de Barenne & McCulloch (1, 3)]. Since a full review of this work (much of which had not then been published) was given two years ago [Fulton (1)], only selected topics will be included herein for review. These will be (i) the eye fields (area 8), (ii) the frontal association region (areas 9–10–11–12), (iii) the face areas (F.4, F.4-s, F.6*a*, F.6*b* and F.3), and (iv) the effects of age on motor functions.

The eye fields (*area 8*).—Kennard & Ectors and Kennard (2) have studied the excitability of the cortical eye fields, confirming earlier work that stimulation causes: (i) conjugate deviation of the eyes toward the side opposite, with a tendency, when the stimulus is strong, toward turning the head in the same direction; (ii) pupillary dilatation; (iii) opening or closing of the lids (different foci); and (iv) lacrimation of the contralateral eye. There is thus evidence of focal representation in area 8, but the foci are less discrete than in area 4.

Ablation of area 8, when unilateral, causes conjugate deviation of the eyes towards the side of the lesion, forced rotation of the body toward that side during locomotor movements, a "pseudo-hemianopia" characterized by failure to heed objects on the opposite homonymous side; but all these effects are transient, disappearing entirely within two or six weeks. When area 8 is removed from both sides, the animal appears dazed, fails to respond normally to objects brought into its field of vision and its facies become immobile as in Parkinsonism. The gaze is "fixed" for the first week or ten days, but thereafter the animal becomes restless, distractable and shows permanent motor hyperactivity so long as it is in a lighted room. When the room is darkened the motor activity ceases (Kennard, unpublished).

Frontal association areas.—The influence of specific ablations of the frontal lobes upon intellectual processes has been studied at length and recently reviewed by Jacobsen (see also Finan). The character of the intellectual deficit which follows bilateral ablation of the areas 9–10–11–12 of Brodmann (Fig. 1) has been described in objective terms by a number of simple procedures such as the delayed reaction test and the stick-and-platform problem, both of which involve temporal behavior and both of which are disturbed following bilateral ablation of the frontal areas in monkeys, chimpanzees, and man. After such lesions the experimental subject tends to become restless and distractable, but it continues to exhibit a lively interest in its immediate surroundings. Jacobsen also observed that chimpanzees after such ablations were seemingly immune to experimental neuroses—being quite undisturbed by failures in discrimination tests.

On the basis of these experimental findings a procedure has been introduced for dealing with human psychiatric cases which involves interrupting the projection fibers from both frontal as-

sociation areas. According to Watts & Freeman [see also Freeman & Watts (1, 2), Lyerly (unpublished) and more recently Rylander of Stockholm], many institutional cases regarded as hopeless have as a result of surgical interruption of their frontal projection become euphoric, cheerful and able to cope with the exigencies of existence. The effects of bilateral frontal lobotomy are now under close scrutiny and are being compared with the results of other procedures such as insulin and metrazol convulsions. It is too soon to pass judgment upon the relative merits or justifiability of any of the three forms of therapeutic treatment,

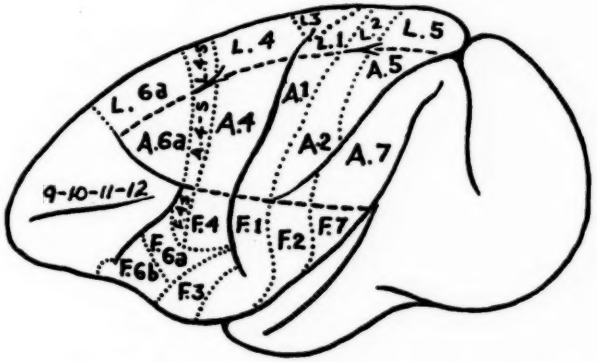

FIG. 1. Diagram of the sensorimotor cortex of the macaque showing the principal cytoarchitectural regions (after Dusser de Barenne, McCulloch & Ogawa).

but the lively interest which these new procedures have aroused indicates the close correlation which is now coming about between experimental physiology of the nervous system and clinical neurology.

The face areas.—The face areas have been little studied since the early work of the Vogts. Dusser de Barenne, McCulloch & Ogawa have investigated the effect of local strychninization of the subdivisions of the face area indicated in Fig. 1. Such activation of any part of the face areas failed to affect the arm or leg areas, save for F.4-s which caused slight suppression of electrical activity of A.4 and L.4. Strychnine applied to F.4-s and to F.1 (postcentral) suppressed electrical activity of F.4, indicating that

F.4 is normally regulated by adjacent regions. Walker & Green, investigating the effects of stimulation of the face areas, have largely confirmed the work of the Vogts in finding that area F.4 caused brief contractions of individual muscle groups, F.6*a* yielding more complex movements of the premotor type, F.6*b* masticatory and deglutatory movements and also reactions of the vocal cords, salivation, etc. They also noted, as had the Vogts, that stimulation of the lower part of F.6*b* caused inhibition of respiration; but this finding is probably to be reinterpreted in the light of Bailey & Sweet's recent disclosures concerning respiratory representation on the orbital surface of the frontal lobe (see above p. 245).

Analysis of the effects of ablating the face areas led Green & Walker to conclude that area 4 sends direct cortical projection to the final motor neurons of the labial muscles, the muscles of the food pouches and muscles of the tongue. Area 6*a* (the premotor) probably has few direct motor projections, while F.6*b* possesses independent projections which are mainly concerned with gross movements of the tongue, fauces and vocal cords. The lower facial musculature is represented almost solely on the contralateral cortex, while the upper facial and pharyngeal and laryngeal have a larger bilateral representation.

Fulton & Dow in their study of the tonic neck reflexes found that these were suppressed by the face areas, especially F.4. In order to release the tonic neck reflexes one must remove F.4 and F.6 in addition to areas A.4 and 6, and L.4 and 6.

Age and motor functions of the cerebral cortex.—Since the corticospinal pathways are only partially myelinated at birth and since the reflex patterns of behavior which characterize motor performance of the newly born primates are unaffected in early infancy by ablation of the motor area, it follows that the cortical level is less important at birth than in the later life. Following removal of areas 4 and 6 from monkeys and chimpanzees during infancy—a procedure which renders an adult almost completely and permanently incapacitated from the point of view of volitional function—Kennard (1, 3) finds little initial disturbance but as the animal grows older signs of deficit become conspicuous. Such monkeys, however, fare far better than would an adult following such a lesion. Evidence of reorganization of motor functions becomes apparent in that certain motor patterns normally regulated by areas 4 and 6 are taken over by the frontal associa-

tion and postcentral regions. Volitional acts such as those essential for feeding, climbing, etc., become possible but isolated movements of the digits never reappear.

Kennard has also observed (3) that spasticity and other forms of augmented postural resistance do not appear following cortical lesions in infancy. Indeed these special release manifestations do not become manifest in the monkey in conspicuous form until the animal is one or two years of age. In a chimpanzee from which areas 4 and 6 were ablated at the age of three months (a lesion which causes intense spasticity in the adult), showed no change in postural resistance for about five months. At six months of age hyperreflexia of the deep reflexes and a positive Rossolimo reaction began to appear, but there was still no increased resistance to passive movement. Slight spastic resistance began to develop toward the end of the first year of life; during the second year it increased still further. It is well known that in human infants cerebral injuries are not at first accompanied by spasticity and that the time of its ultimate appearance is highly variable.

General Properties of Central Nervous Tissue

In addition to studies of specific functional levels, a number of highly important disclosures have been made during the last two years concerning the general properties of central neurons. These relate to correlations of the electrical and chemical changes with the excitability cycle of central neurons, to the enzyme systems of neurons and to the chemical agent acetylcholine.

The excitability cycle of central neurons.—Lorente de Nó (2) and Dusser de Barenne & McCulloch (4) have made a fundamental correlation between the excitability cycle of central neurons and their temporal, electrical and chemical characteristics. Lorente de Nó has established that synaptic delay in central neurons is of the order of 0.5 to 0.7 msec. This applies to motor neurons and probably also to internuncials, and since the refractory period of the dendrites is greater than the synaptic delay, it means that temporal summation cannot occur at a single synapse.[4] Since many

[4] Temporal summation, as originally described by Sherrington, from repetitive stimulation of an afferent end-organ or an afferent nerve, occurs and is of basic importance in the physiology of the nervous system, but the temporal effects are made possible by the spatial convergence of many synaptic terminals upon one or more central neurons. Temporal summation from impulses arriving at the single synaptic terminal is impossible because of the brief duration of the local synaptic excitatory process.

synaptic terminals converge on a motor neuron, spatial summation is possible. According to the electrical theory of transmission, the impulse reaching a synaptic terminal brings about during the 0.5 msec. synaptic delay, an accumulation of unspecified ions that cause focal depolarization of the contiguous cell membrane; according to this hypothesis the process is entirely akin to the local excitatory process in peripheral nerves (where no one has postulated the necessity of a special transmitter between the end of the stimulating electrode and the excitatory membrane of the axis cylinder). But when cells are activated repetitively over a period of time intra- and extracellular agents accumulate which affect the resting excitability of the cell. The pH, for example, changes, and Dusser de Barenne, McCulloch & Nims find that excitability of the cell is enhanced (giving rise to the phenomenon of facilitation) when the pH shifts to the alkaline side, at which time a negative voltage drift can also be demonstrated which might possibly be a negative after-potential. Similarly diminution of excitability occurs, as in the phenomenon of extinction, when the pH shifts to the acid side; with such a change there also occurs a positive voltage drift, which might be a positive after-potential in the affected neurons. Dusser de Barenne & McCulloch (4) have not attempted to correlate the phases of the excitability cycle with other chemical agents known to be associated with nerve activity. Bronk, however finds that an excess of potassium around a nerve cell or low concentrations of acetylcholine when brought similarly to the neuron as an extracellular agent, cause greatly increased excitability and that an excess of either potassium or of acetylcholine (both of which are liberated during synaptic activity) may lead to actual discharge of the cell. Hence it is obvious that environmental changes of the cell, be they due to specific chemical agents or to alterations in the crystalloid balance (e.g., in the ratio of potassium to calcium) have an immediate effect upon the excitability cycle and hence upon synaptic transmission.

Choline esterase in central neurons.—The prominence recently given to acetylcholine in the theories of synaptic transmission give special significance to the important studies of Nachmansohn (1, 2, 3) on the distribution of choline esterase in the central nervous system. If acetylcholine proves to be one of the molecules concerned in the activation that occurs when an impulse traverses

a synapse, then it is highly important than an enzyme be present which will immediately destroy this powerful agent and prevent its continuous action through diffusion into the blood stream. Dr. Nachmansohn has kindly provided the following summary of his work bearing upon this problem.

At motor end plates there exists a concentration of choline esterase high enough to split acetylcholine liberated by nerve stimulation during the refractory period. The existence of such a peculiar enzymatic system induced Nachmanson (2) to investigate whether a similar special concentration of choline esterase exists at ganglionic and central synapses. The enzyme concentration of the superior cervical ganglion of cats is several times as high as that of the preganglionic fibers. If the difference of enzyme concentration in this nearly homogeneous tissue is attributed to a special concentration of the enzyme at synaptic regions, the amount of acetylcholine which can be split at these foci during the refractory period of the ganglion would be many times as high as that liberated in the ganglion by a single maximal shock, according to the figures of Feldberg & Vartiainen. If, therefore, only a small fraction of the difference in enzyme concentration found between ganglion and fibers has to be attributed to a concentration of the enzyme around nerve endings the enzymatic system of the ganglion would satisfy one requirement of a transmitter function of acetylcholine: the rapid removal of this substance.

In the abdominal chain of lobsters (*Homarus vulgaris*), which represents the central nervous system of these animals, the enzyme is likewise several times more highly concentrated in the regions where cell bodies exist and synapses are accumulated than in the fibers between them.

In brain and spinal cord the concentration of choline esterase is always low in white and high in gray matter. In the gray matter the enzyme is unevenly distributed. The values of Q·Ch.E. (mg. of acetylcholine hydrolysed per unit of time and tissue) vary, e.g., in the ox brain from 2.0 to 3.0 in the cortex to about 70 in the nucleus lentiformis (putamen). The values are different not only for each center, but also for each species. In the species examined, rabbit, dog, ox, and man, concentrations generally decrease with the increase of brain mass. The most remarkable fact appears to be the great constancy of the values for each center and each species in contrast to the great variations from one center to the other and one species to the other. The figures obtained indicate that the concentration of the enzyme at central, as well as at ganglionic synapses, is high enough to remove, during the refractory period, an amount of acetylcholine which could account for a transmitter function.

The physiological significance of this peculiar enzymatic mechanism is emphasized by the fact that in growing animals a relationship exists between the time at which central synapses begin to function and the time at which the high concentration is reached. In brain of chicken, it increases rapidly during the last four days of incubation and is high at hatching. In newborn rats and rabbits the concentration is low, and increases to high values during the first three weeks after birth. In guinea-pigs, which are fully developed at birth, the concentration at that period is high and does not rise more during the first three weeks.

In view of the high concentration of choline esterase at central synapses it is significant that strychnine strongly inhibits purified solutions of the enzyme [Nachmansohn (3)]. Such purified solutions were prepared by Nachmansohn & Lederer from the electric organ of *Torpedo*, which contain more enzyme than any other organ examined so far. The anti-esterase power of strychnine is strong enough for the assumption that the intoxication by the drug may be in relation with its action on the enzyme. Such an interpretation would fit with Sherrington's conception that strychnine augments central excitatory processes without affecting inhibition.

Fright reaction and acetylcholine.—Denervated striated muscles become highly sensitized to acetylcholine. Bender (1, 2) has observed that the denervated extraocular (those supplied by the third nerve) or facial muscles of monkeys exhibit involuntary contraction during states of anger and fright (the "fright reaction"). Indeed a threatening gesture made toward such an animal is followed by a slow, involuntary contraction of the muscles in question, the response continuing for a period of thirty to forty seconds. The reaction is augmented by physostigmin and is readily reproduced by intravenous injection of small quantities of acetylcholine. Epinephrine failed to reproduce the phenomenon. Bender & Kennard calculated that the concentrations of acetylcholine reaching denervated muscles in concentrations of less than 1×10^{-9} gm. per cc. of blood are sufficient to cause the fright reaction. The reaction was unaffected by intracranial severance of the fourth, fifth, and sixth cranial nerves and was likewise wholly unaffected by removal of the cervical sympathetic chain including the superior cervical ganglion. The effect therefore can not be attributed to local release of acetylcholine, but may be due to liberation of acetylcholine into the general circulation [see also Bender & Fulton (1, 2)]; the phenomenon is entirely parallel to the well-recognized liberation of epinephrine in emotional states.

In comparing cats and monkeys Bender (3) points out further:

Since the sympathetically denervated pupil dilates with adrenalin, and the denervated facial muscles contract with acetylcholine they may be used as indicators for exogenous or endogenous adrenalin and acetylcholine. With fright, the denervated pupil dilated strongly, whereas the denervated facial muscles contracted feebly in some but not in all cats. In the frightened monkey the denervated pupil did not dilate but the denervated facial muscles contracted vigorously in every instance. The monkey's pupil dilated slightly with fright when both the oculomotor and cervical sympathetic nerves were sectioned. Parenteral injections of cocaine reversed the fright reaction in the monkey, i.e., the denervated pupil dilated while the denervated facial muscles did not contract. Six

seconds after intravenous injections of large doses of acetylcholine (0.04–0.10 mgm.) into the cat there occurred a contraction of the denervated facial muscles; 15 seconds later a pronounced dilatation of the denervated pupil followed. This indicated a delayed or reactive adrenalin effect. Intravenous injections of large amounts of acetylcholine into the uneserinized or eserinized monkey (1.0–2.0 mgm.) caused the usual contraction in the denervated face, but no dilatation of the denervated pupil such as was observed in the cat. In the same monkey intravenous injections of large amounts of adrenalin, however, produced marked dilatation of the sympathectomized pupil within 6 seconds and a definite contraction in the denervated facial muscles within 60 to 90 seconds. This indicated a delayed or reactive acetylcholine effect. There was no such effect in the cat. Intravenous adrenalin in the cat produced dilatation of the denervated pupil but no contraction in the denervated face.

These observations indicate that both parts of the autonomic system are active in each species and that the sympathetic and parasympathetic systems are in equilibrium. The cat, however, is predominantly sympathetic, while the monkey is predominantly parasympathetic in its reactions.

It thus follows from Bender's evidence that circulating acetylcholine is to be reckoned with as one of the basic agents underlying the physiology of emotional expression. Its presence in the blood stream obviously accounts for many phenomena of emotional states not readily accounted for by the liberation of epinephrine alone. The appearance of acetylcholine in the blood stream is, however, without immediate bearing upon the synapse controversy since many other substances also make their appearance in the blood in times of stress.

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THE AUTONOMIC NERVOUS SYSTEM

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Autonomic Nerves

The behavior and properties of autonomic axons were the subject of several studies. Grundfest concluded that the fibers contributing to the B component of the spike potential of preganglionic nerves are quantitatively so different from other fibers as to justify the designation of the B group as an entity qualitatively distinct from the A (cf. Gasser & Grundfest) and the C (cf. Grundfest & Gasser) groups. A similar conclusion was reached by Bishop & O'Leary. Graham found that cathodal or anodal polarization of C fibers modifies both the spike potential and the after-potentials. Maltesos & Schneider reported a wide range of electrical excitabilities for the fibers in different autonomic groups stimulated by means of an alternating current.

The previous studies emphasize quantitative differences between autonomic and somatic nerve fibers, and between different groups of autonomic elements. They do not, however, bring out any qualitative features specific to any nerve elements. Those studies are concerned with the properties of axons as conducting agents. The classic law of the non-specificity of nerve impulses remains therefore unquestioned. Recent studies, on the other hand, prove that nerve elements may differ qualitatively from one another in the presence or absence of substances (acetylcholine or epinephrine) concerned with transmission at nerve-nerve or nerve-muscle junctions. A relative degree of specificity of neurons is thus suggested.

Dale's proposal that certain neurons be classified as adrenergic and others as cholinergic received direct support in Lissák's (2, 3) and Cannon & Lissák's studies. Acetylcholine, but not epinephrine, is contained in and liberated by stimulation from some autonomic and somatic nerves. Conversely, epinephrine, but not acetylcholine, is present in some autonomic neurons. It is of interest that the nerve fibers where acetylcholine was found were precisely those which had been shown by previous studies to act at their periph-

eral junctions by liberation of this substance, a similar relation holding for the fibers containing epinephrine. Whether or not these substances intervene in the process of conduction of nerve impulses is a question for future work. A negative answer appears more likely with the present incomplete data. Hellauer's observations agree with those of Lissák: adrenergic nerves contain little or no acetylcholine; it is interesting that they contain, on the other hand, relatively large amounts of cholinesterase.

Lissák's (3) report on the liberation of acetylcholine by stimulation of cholinergic nerve trunks agrees with the results of Chang *et al.* (1, 2). The similar previous findings of Calabro and of Binet & Minz (1, 2), which had been contested by Gaddum, Khayyal & Rydin, are thus fully confirmed. Lorente de Nó's observation that stimulation of the vagus may lead to the release of acetylcholine into the veins from the nodosum ganglion is a further instance of the same phenomenon. As Lissák (3) points out, however, Lorente de Nó's analogous results upon stimulation of the postganglionic cervical sympathetic fibers remain unexplained, for these fibers are mainly or exclusively adrenergic in the cat.

Nerve-effector Junctions

Since the concept of humoral transmission of nerve impulses at autonomic neuro-effector junctions was generally accepted a few years ago, the attention of the workers in this field turned to some of the questions which that concept implies, especially the nature of the chemical mediators, their mode of production and release, and their mode of action on the effectors. Although several publications bearing on these questions have appeared in the past year, it does not seem to the reviewer that any definite answers are yet available.

That sympathin differs from epinephrine was shown by Cannon & Rosenblueth (1) in 1933. They suggested that epinephrine is released by adrenergic nerve impulses, but is modified in one of two ways at the effector so that there ensues either a sympathin E, with excitatory action, or a sympathin I, with inhibitory effects. Although this theory has not gained explicit recognition, recent hypotheses do not differ significantly from its broad outline. Thus, Bacq's (1, 3) suggestions that sympathin E is norepinephrine, i.e., a demethylated epinephrine, and that sympathin I is "adre-

noxine," i.e., epinephrine modified by catecholoxidase in the inhibited structures, are specific variants of the original general theory.

As regards Bacq's first suggestion, Gaddum & Kwiatkowski find that the substance released by stimulation of the cervical sympathetic of the rabbit, a fairly pure source of sympathin E, resembles epinephrine rather than norepinephrine in its properties. Several difficulties have likewise arisen for the acceptance of Bacq's second hypothesis. Lissák (1) was unable to confirm some of Bacq's results. Goffart (2) concludes that the action of "adrenoxine" on the isolated rabbit intestine differs from that of epinephrine or sympathin. Ungar & Parrot (2) report that "adrenoxine" stimulates the guinea pig and rat intestine, instead of exerting an inhibitory effect. Finally, Blaschko & Schlossmann deny that Bacq's "adrenoxine-effect" is due to the action of pure catecholoxidase on epinephrine.

Hermann *et al.* (3) reported that the hypertension elicited by prolonged continuous uniform intravenous injections of epinephrine is not sustained, but declines progressively. Morin found a similar phenomenon with regard to the inhibition of excised intestine and attributes the decline of the response to a change in the reactive properties of smooth muscle. Morin's observations were confirmed by Tiffeneau & Scheiner (1). Analogous declines of responses to acetylcholine were studied by Scheiner for the blood pressure, by Tiffeneau & Scheiner (2) on several smooth muscles, by Moisset de Espanés & Martinez on the toad heart, and by Tournade & Chardon (1) for the pressor nicotine-like action of acetylcholine in atropinized dogs. Segura suggested that vagal escape of the heart may be explained by these phenomena.

Secker reported that adrenalectomy leads within a few hours to failure of the responses of the nictitating membrane, of the intestine, and of the blood vessels to repeated stimulation of the corresponding sympathetic nerves. Injections of epinephrine led to a slight temporary recovery of these responses. Extracts of adrenal cortex were far more efficient in restoring the function of the nerves. He suggests that the adrenal cortex is concerned in the formation of the chemical mediator of sympathetic nerve impulses (cf. Armstrong *et al.*). The reviewer wishes to point out that in numerous experiments performed in this laboratory in which the

cervical sympathetic of adrenalectomized cats was stimulated repeatedly, no significant decline of the responses of the nictitating membrane was observed over a period of several hours. Indeed, an attempt to duplicate Secker's experimental conditions (Dempsey, unpublished) likewise gave negative results in three cats.

The action of drugs having differential blocking effects on the responses to sympathetic nerve stimulation and to epinephrine was the subject of several studies. It becomes increasingly evident from previous reports and from those cited below that the action of these drugs is different in various systems. No general theory has been suggested which covers adequately all the data available. Raymond-Hamet found an inversion of the effects of epinephrine on the kidney vessels by corynantheine hydrochloride, while the reflex response to occlusion of the carotid arteries was unaltered. He states that this observation is oppposed to the view that drugs of that type render the reacting cells impermeable to injected epinephrine [cf. Cannon & Rosenblueth (4)]. Hill & Myers were unable to confirm Shen's claim that 933F (piperidomethyl-3-benzodioxane) inverts the action of epinephrine on the frog heart. They found only slight changes in the responses of frog's and cat's hearts both to epinephrine and to accelerator impulses. Daels reported that while 933F may decrease or abolish, but not invert, the inhibitory action of epinephrine on the guinea pig or non-pregnant cat uterus, it can invert the normally contractile responses of rabbit or pregnant cat uterus. Hermann *et al.* (4) described a reversible restoration of the hypertensive action of epinephrine during continuous injections of the hormone into dogs treated with 933F. Similar reversals of the action of continuous injections of epinephrine and acetylcholine into animals treated with yohimbine and atropine, respectively, were found by Tiffeneau & Scheiner (3).

Clark & Raventós analyzed quantitatively the responses of several effectors to sympathetic stimulation. They confirmed the report of Rosenblueth & Morison that the curves relating the amplitude of the response with either graded doses of epinephrine or varying frequencies of stimulation are superimposable. They likewise confirmed Bacq's (2) finding that pyrogallol increases the duration of the responses of the nictitating membrane to epinephrine; they failed, however, to substantiate Bacq's statement that the amplitude of the responses is also increased. Clark & Raventós

explain the concentration-response and the frequency-response curves as indicating that the destruction of sympathin and of epinephrine follows a monomolecular course. Since they find that pyrogallol does not change the summation effects of sympathetic stimulation, they conclude that the mechanism by which sympathin is removed is not of the same character as the oxidation of epinephrine, i.e., these results bring out a further difference between epinephrine and sympathin.

In a further study of the effects of successive vagal nerve volleys delivered to the turtle heart at various time intervals, Fredericq (2) suggests the following explanation for the secondary refractory period which he (1) had previously described. The quantum of acetylcholine liberated by a first nerve volley after producing its chronotropic and inotropic effects undergoes a chemical change. One of the substances which ensues acts as an "antimediator," that is, it prevents the liberation of a further quantum by a second nerve volley, hence the secondary refractory period.

Gilson reported that the electrical excitability of the turtle atrium is decreased during vagal inhibition. Although the chronaxie is shortened, the rheobase is increased. The threshold is thus higher for all but very brief shocks. These changes of excitability are explainable as resulting from an increased accommodation of the cardiac muscle to the stimulating currents. This work confirms and extends the previous observations of Ashman & Garrey.

In a study of the appearance of chemical mediators in the aqueous humor upon stimulation of the corresponding autonomic nerves, Luco & Lissák showed that activation of the postganglionic sympathetic fibers after degeneration of the cut preganglionic axons elicits a greater concentration of sympathin than on the normal control side. This finding is in keeping with the observations of Goffart (1) and of Goffart & Bacq, that the acetylcholine content of the digestive tract increases after section and degeneration of the vagal fibers.

Vincent did not observe any lasting storage of acetylcholine or choline in several organs examined after repeated injections of acetylcholine to animals. The renal output of choline was likewise only transiently and slightly increased after the injections. He concludes that choline is metabolized by the organism. Trethewie did not find any evidence of a "precursor" or "complex" in cells

from which acetylcholine would be released. He concluded that the internal structure of the cell, and not the integrity of the outer membrane, determines its capacity for holding in its substance the active principle. These views oppose the concept of "free" and "bound" acetylcholine proposed by Corteggiani and recently defended by Corteggiani *et al.*

Autonomic Ganglia

The problem of transmission of nerve impulses at the synapses in autonomic ganglia was the subject of intensive study and discussion. The following specific questions are at issue. Is transmission across those synapses similar in mechanism to the conduction of a nerve impulse along an axon, or is there a qualitatively specific process of synaptic transmission? The defenders of electric transmission adopt the first alternative; the advocates of chemical postsynaptic activation affirm the second one. Is transmission fundamentally due to a unique factor—chemical or electrical—or are there several excitatory agents? The pluralists favor the latter alternative. Can postsynaptic excitation be supraliminal, and thus outlast the delivery of presynaptic nerve impulses and result in after-discharge? The electrical theory does not explain after-discharge from autonomic ganglia satisfactorily. What is the role of the presynaptic action potential in transmission? According to the electrical theory, it is the transmitter; the chemical theory denies that its amplitude is adequate for postsynaptic stimulation and assumes it to be concerned mainly or exclusively with the liberation of the mediator. What is the role of the acetylcholine liberated by presynaptic stimulation? The chemical theory states that it is the transmitter, while according to the electrical concept, it is an adjuvant of transmission, counteracting the onset of fatigue and exerting a local vasodilator influence [Eccles (3)]. Alternatively, it could be a non-specific metabolic product (Lorente de Nó), or finally, a regulator of transmission (Schaefer & Haass).

One of the early arguments adduced against the chemical theory was that acetylcholine could not be removed promptly enough after liberation to account for the usual absence of after-discharge [see Eccles (3)]. A careful study of Nachmansohn leads him to the conclusion that the amount of acetylcholine liberated

by a presynaptic nerve volley would be hydrolyzed by cholinesterase during the refractory period.

That after-discharge may take place at the superior cervical ganglion was shown by Eccles (1) after treatment with physostigmin. Larrabee & Bronk find marked persistent discharges after brief rapid preganglionic stimulation, without the use of any drug. Bronk summarizes other long-lasting effects of presynaptic nerve impulses.

The problem of the nature of ganglionic after-potentials and of their correlation with facilitation and inhibition of the effects of presynaptic nerve impulses was studied by Lloyd (1, 2). He (2) supports Eccles' (2) claim that negativity of the ganglion cells with respect to their axons results in facilitation, while positivity is attended by inhibition. Some of the data presented by Lloyd (2) do not appear to justify that claim. Thus, although veratrine greatly increased the negative after-potential of the ganglion cells, he states that this greater negativity was not reflected by facilitation. In discussing some of the observations of Rosenblueth & Simeone (2) which led them to question the correlation under discussion, Lloyd (2) qualifies as illusory the increase of spike potentials frequently seen at the peak of the positive after-potential of a preceding conditioning volley. He attributes the apparently larger spikes exclusively to an increase of the negative after-potential. For such an explanation to be valid, it would be necessary to assume [cf. fig. 8 in Lloyd's paper (2)] that the negative after-potential attains its maximal value instantaneously after the initiation of the spike. This assumption is in contradiction with the time course for after-potentials described by Gasser and by Eccles (2). Lloyd did not consider other difficulties mentioned by Rosenblueth & Simeone (2) which appear in the evaluation of the data on facilitation and inhibition, namely, possible changes in the presynaptic test volleys, unavoidable sources of error in the measurement of the test responses, and finally possible changes in the spike magnitude of the fibers contributing to the test responses. These difficulties have been again emphasized by Bronk. The opinion of the reviewer is, therefore, that although changes in the potential of the ganglion cells may modify their responsivity to preganglionic impulses, other independent factors may overwhelm this influence, as Rosenblueth & Simeone pointed out. Bronk's

view appears to be similar. Indeed, Bronk's demonstration that the ganglionic responses to acetylcholine are modified during the period of development of after-potentials in a ganglion indicates that no discriminating conclusions as to the mode of transmission may be drawn from the present data on excitability changes.

Coppée & Bacq found that transmission through the superior cervical ganglion fails during Wallerian degeneration of the preganglionic fibers at a time when the action potentials of these fibers are still full-sized. A concomitant analysis by MacIntosh of the acetylcholine content of the ganglia indicated that failure of transmission could be correlated with a significant diminution of the concentration. Coppée & Bacq conclude that acetylcholine is indispensable for transmission of the ganglion but add that this conclusion does not imply that the electrical theory of transmission should be dismissed. The latter statement is difficult to understand. If acetylcholine is indispensable for transmission the present electrical theory, i.e., that synaptic transmission is similar to axon conduction, is inacceptable. Chauchard (1) attributes the precocious failure of transmission during Wallerian degeneration to heterochronism due to the increase of the chronaxie of the postganglionic elements.

Rosenblueth & Luco found that the impairment of transmission of motor nerve impulses to skeletal muscle which takes place during fatigue (fourth stage of transmission) is followed by renewal of activation (fifth stage) if the repetitive stimulation is prolonged sufficiently. A similar phenomenon was reported by Lanari & Rosenblueth for transmission at autonomic ganglia. The decline of response of the nictitating membrane and the iris upon prolonged rapid stimulation of the cervical sympathetic was followed by a late persistent increase. The changes of heart rate produced by vagal stimulation showed the same sequence. The well known resemblance between the transmission processes at neuromuscular junctions and at ganglionic synapses is again emphasized by these parallel observations.

A study by Rosenblueth, Lissák & Lanari of changes in the presynaptic and postsynaptic elements which attend the appearance of the fourth and fifth stages showed that the acetylcholine liberation from the presynaptic fibers is decreased during the fourth stage and increases when the fifth stage is reached.

The present status of the problem of synaptic transmission at autonomic ganglia appears to be the following: A purely electrical theory does not account satisfactorily for the data. Synaptic delay, after-discharge, curarization, the fourth and fifth stages, and Wedensky inhibition do not seem to be reasonably explained by that theory. That acetylcholine is an indispensable step in the process is quite probable. Failure of transmission during fatigue, curarization, and early Wallerian degeneration seem to be due exclusively to insufficiency of acetylcholine liberation. That the concept of acetylcholine mediation is incapable, however, of accounting for all the phenomena of transmission is likewise quite certain. Some of the long lasting changes mentioned above and the post-tetanic modifications [cf. Cannon & Rosenblueth (3)] are not explained by that concept. Many more data appear necessary before a comprehensive theory may be formulated. Bronk's injunction is admirably timed that, in the defense of a given theory, there is danger of ignoring relevant factors known to influence synaptic transmission: the presynaptic spike potential, acetylcholine, ionic changes, oxygenation, changes brought about by previous activity, and others.

As additional facts concerning autonomic ganglia, the following may be mentioned. Marrazzi (1) reported a direct inhibitory action of epinephrine on the superior cervical ganglion. He (2) suggests that such inhibition may produce a self-limitation of sympathetic hyperactivity during homeostatic adjustments. Kahlson & MacIntosh confirmed the finding of Brown & Feldberg (1) that the superior cervical ganglion can synthesize acetylcholine during prolonged stimulation. Lanari & Luco found that strychnine has exclusively a depressant action on sympathetic ganglia. The contrast between this depressant effect and the excitatory action of strychnine in the spinal cord suggests that there may be fundamental differences in the mode of transmission of nerve impulses at different synapses.

Potassium Ions

That potassium ions may play a fundamental role in ganglionic transmission is strongly suggested by several studies. It is known, for instance, that potassium increases the responses of the superior cervical ganglion to single submaximal preganglionic volleys, that

it liberates acetylcholine from innervated ganglia, that it stimulates normal and denervated ganglia to discharge, and that in large doses it paralyzes transmission through the ganglion [Brown & Feldberg (2)]. It has been also shown that the innervated ganglion loses potassium during stimulation, a change which does not occur in denervated ganglia (Vogt). Indeed, on the basis of some of these data, Eccles (1) suggested that potassium ions were the transmitters of preganglionic nerve impulses. Although the role of potassium in transmission remains unknown, because of these significant suggestions, the data reported during the year on this topic are grouped in this section.

Larrabee, Brink & Bronk, confirmed the observation of Brown & Feldberg (2) that moderate concentrations of potassium facilitate the action of submaximal preganglionic volleys in sympathetic ganglia, while strong concentrations block synaptic transmission. They emphasize that these changes need not be due to a specific action on the synaptic mechanism, since they are similar to the alterations of electrical excitability produced by potassium on nerve trunks. Brown & MacIntosh, likewise, found that potassium chloride injected into the superior cervical ganglion activates not only the postganglionic, but also the preganglionic elements. The release of acetylcholine by potassium could thus be due to the non-specific activation of the preganglionic nerve endings.

Hazard reported that sparteine has differential effects on the nicotine-like actions of acetylcholine and potassium. The hypertension elicited by acetylcholine after atropine is abolished or even inverted by sparteine, whereas that produced by potassium is reinforced. A similar differentiation was observed by Hazard & Wurmser by means of magnesium salts. While magnesium ions only decreased the nicotine-like action of acetylcholine (after atropine), they abolished entirely the hypertension produced by potassium. These observations are reinforced by Cicardo's comparative study of the action of potassium ions and acetylcholine on toad's skeletal muscle. Denervated muscles, well known to be hypersensitive to acetylcholine, were hyposensitive to potassium. Cobra venom in doses sufficient to block the transmission of motor nerve impulses abolished likewise the responses to acetylcholine but did not prevent the contractions caused by potassium.

Hermann *et al.* (1) found that potassium raises the blood pressure, both because it stimulates the vasoconstrictor centers and because it promotes adrenal secretion. The peripheral effect developed with doses much smaller than those necessary for activation of the centers. They (2) also reported that stimulation of the adrenal medulla is produced by all alkaline ions excepting sodium. Potassium was unquestionably the most effective; next came rubidium and ammonium.

Autonomic Control of Effectors

Malméjac, Donnet & Jonesco observed exclusively constrictor responses to epinephrine in the skin vessels of dogs. No dilatations were obtained with any doses of the hormone. Similar observations were made by Goetz on cats and dogs. The vasoconstrictor reactions of the paw were quite independent of the blood pressure changes; thus, marked constriction was seen with no alterations of blood pressure; or a rise of blood pressure could attain its maximum before any constriction could be detected in the paw. Goetz concludes that the reaction of skin vessels is not of primary importance in producing the first elevation of the blood pressure after epinephrine and that epinephrine acts more as a blood distributor than as a blood pressure augmentor agent. Forbes, Schmidt & Nason reported further evidence of a parasympathetic vasodilator innervation of cerebral vessels in the parietal region of the cat.

Katz & Jochim found only cholinergic coronary vasodilator fibers in dog's vagi. These fibers had a tonic activity. There was no evidence of cholinergic constrictors. The sympathetic supplied both adrenergic dilators and adrenergic constrictors to the coronary vessels. Although both sets of sympathetic fibers were found tonically active, the effects were predominantly vasoconstrictor. According to this careful and important study the innervation of the coronary vessels is similar to that of other systemic vascular territories, and not radically different, as has been quite generally accepted hitherto.

Troisier, Bariéty & Kohler observed that epinephrine and ephedrine produce an increase of intrapleural pressure and a concomitant decrease of the amplitude of its respiratory oscillations. These phenomena occurred without any significant change of the

pneumogram. The authors attribute them to modifications in the lungs. A more detailed study of vascular changes in the lungs was reported by Petrovskaia. In isolated pig's lungs, epinephrine reduced the arterial pressure in fresh preparations and later caused an augmentation of this pressure; ergotoxine reversed the pressor effect. Small doses of acetylcholine lowered, and larger doses raised the pulmonary arterial pressure in ergotoxinized preparations.

Babkin, Hebb & Sergeyeva obtained pancreatic external secretion by stimulation of the splanchnic nerves. This secretion was comparable to that elicited by activation of the vagal secretory fibers. Atropine abolished the phenomenon; physostigmin enhanced it, while cocaine had no effect. Injections of epinephrine did not elicit pancreatic secretion. Acetylcholine could be demonstrated in the venous blood of the gland after stimulation of the splanchnics. Babkin *et al.* conclude that the secretory fibers concerned are cholinergic. Tests with nicotine showed that there is a peripheral relay beyond the celiac ganglion. The positive results on the release of acetylcholine into the venous blood are in opposition to the observations of Gayet, Minz & Quivy, in which stimulation of the splanchnics led to the appearance of the mediator in the blood from the stomach and occasionally from the intestine, but never from the pancreas.

Luco (2) studied the effect of epinephrine in counteracting fatigue of normal striated muscles stimulated indirectly and of denervated muscles stimulated directly. The depressant action occasionally encountered disappeared after ergotoxine. He attributed such depression to vasoconstriction. The positive results confirm the observations of Cannon & Nice and of Gruber. Luco found in addition that epinephrine increases the responses of denervated muscles to acetylcholine and that stimulation of the cervical sympathetic also increases the responses of facial muscles with a degenerated motor nerve supply. Bülbring & Burn found that during a muscular tetanus the constrictor response of the muscle vessels both to sympathetic stimulation and to epinephrine is present but decreased. The tension maintained by a muscle during a tetanus is augmented by an increased blood flow and diminished by a decreased blood flow. Although stimulation of the sympathetic during muscle work diminished the blood flow, it nevertheless increased the tension. Similar relations hold for

epinephrine. The Orbeli phenomenon, therefore, is obviously not due to vascular changes.

Libelli reported contractions of striated muscle in the rabbit's ear upon stimulation of the cervical sympathetic. The results were uninfluenced by a moderate dose of curare. Libelli interprets this reaction as the counterpart of the motor disturbances (asymmetrical position of the ears) described by Ducceschi after unilateral cervical sympathectomy. Mies observed a decrease of the demarcation potential of striated muscle of frogs and rabbits when the sympathetic nerve supply was stimulated. In rabbits the red muscles appeared to be supplied mainly by adrenergic nerves and the white muscles by cholinergic fibers. The results of Libelli and of Mies may be due to indirect effects of the chemical mediators released by stimulation of the vasomotor nerves to skeletal muscle. The probability of such effects being direct, i.e., due to an autonomic innervation of the striated muscle fibers, has been rendered minimal by much careful previous work, morphological and physiological, which was reviewed by Hinsey in 1934.

Gauer & Kramer found that epinephrine had no effect on the consumption of oxygen by the heart, except when the cardiac activity was stimulated; there was thus no evidence of a direct effect of epinephrine on the cardiac metabolism.

Ungar & Parrot (1) have reopened the problem of the nature of the chemical mediator of dorsal root vasodilator impulses. They find that an ether-soluble substance, more stable than acetylcholine and capable of inhibiting excised intestine, is released into the bloodstream by lumbar dorsal root stimulation. They suggest that this substance may be the chemical mediator in question. Since Wybauw presented convincing evidence that acetylcholine is also released by dorsal root stimulation, Brown's suggestion is important, that two substances may be liberated by such stimulation, one at the sensory endings and the other at the vascular terminals.

Autonomic Reflexes

Crouch & Thompson reported responses of various autonomic effectors upon electrical stimulation of different points in the motor and premotor cortical regions of cats, dogs, and monkeys. No definite cortical points were found from which certain limited reactions could be elicited. Neither were any separate foci for

sympathetic and parasympathetic functions encountered. A lack of precise localization is thus emphasized. It should be remembered, however, that Morison & Rioch found relatively sharp localization of the cortical regions whose stimulation facilitates or inhibits reflex responses of the nictitating membrane of the cat.

Hare & Geohegan found that the optimum frequency for the autonomic responses to electrical stimulation of the hypothalamus is around several hundred per second. Such high frequency is in marked contrast with the much slower rates (20 to 30 per sec.) which yield optimum effects in many autonomic effectors (Rosenblueth). Hare & Geohegan found, furthermore, that changes in frequency in some instances reversed the sign of the response, i.e., if a low frequency produced a fall of blood pressure, high frequency stimulation of the same area could cause a rise of arterial tension.

Wang & Harrison reported that stimulation of the anterior hypothalamus activates the bladder both through the sacral autonomic and through the hypogastric nerves. Harrison, Wang & Berry brought evidence that the hypothalamic vasomotor efferent pathways have both crossed and uncrossed components. The impulses could descend directly to the spinal cord, or cross in the brain stem or in the spinal cord below the cervical segments. A double crossing for some of the impulses was also assumed, first in the brain stem and then through a spinal commissural system.

Langworthy & Rosenberg described a midbrain center controlling tonically the smooth muscle of the rectum. A transection just cephalic to the posterior corpora quadrigemina resulted in a hyperexcitability of the rectum to stretch stimuli; strong contractions expelled a balloon inserted for recording purposes. After a transection through the medulla, on the other hand, the stretch responses were lost and the wall acommodated to a larger volume than normal.

Freeman & Jeffers studied the efferent pathways involved in the production of hypertension by increased intracranial pressure. The results of a series of partial sympathectomies led them to the conclusion that the influence of the sympathetic on the heart, nervous or humoral, is indispensable for the development of such a hypertension.

Yi observed that stimulation of several afferent nerves caused blood pressure falls in decerebrated animals. The reflexes were not abolished by cauterization of the myelencephalic pressor center,

but disappeared when the depressor area around the obex was destroyed. Injections of ergotoxine or complete removal of the sympathetic chains likewise abolished the responses. Yi concluded that there is a medullary independent depressor reflex center which functions by inhibiting sympathetic constrictors. It may be pointed out that stimulation of sympathetic dilators is not excluded by these experiments. The evidence from ergotoxine is not critical, for, as is well known, the drug abolishes all vasomotor reflexes.

Darrow & Gellhorn reported that epinephrine, whether injected or secreted by the adrenal glands, leads to a decrease of autonomic reflexes, attributed to diminished excitability. No controls are mentioned, however, which would indicate the relative importance of central, ganglionic, or peripheral effects. Haas compared the effects of various drugs on temperature, blood sugar, and differential blood count, when injected intravenously and intracisternally. Picrotoxine and epinephrine produced greater action by the intracisternal, acetylcholine by the intravenous route.

Youmans, Meek & Herrin found that inhibition of the motility of the jejunum caused by a sudden distension is accomplished primarily by means of reflexes over the extrinsic nerves, and only secondarily through the intrinsic nerve elements. Ury & Gellhorn concluded that the normal pupillary dilatation in response to pain is almost exclusively due to parasympathetic inhibition and that it is only in certain experimental conditions, e.g., injections of metrazol, that sympathetic discharges may materially contribute to such dilatation. Anoxia was found to decrease considerably the reflex responses.

Downman *et al.* studied reflex vasoconstriction in the paws of the cat following stimulation of various afferent nerves. Maximal constriction could be obtained with stimuli which produced a rise, a fall, or no change in blood pressure. Removal of the sympathetic pathways abolished the responses. Summation of subliminal stimuli, applied either to the same or to two different afferent nerves, was obtained. Bernthal & Motley recorded the reflex vasomotor reactions of the submaxillary gland upon chemical stimulation of the carotid body. In nine dogs out of eleven, cervical sympathectomy abolished these reactions. In the other two animals residual reactions persisted, mediated presumably by the par-

asympathetic supply. These observations emphasize that reciprocal innervation is not invariably present in autonomic reflexes.

Barron & Matthews (1) repeated some of Toennies' observations on reflex discharges from the spinal cord over the dorsal roots. They could obtain some such reflex discharges in animals with a normal spinal cord temperature, but only in small number. Cooling the cord led to markedly increased responses. They conclude that in the normal animal "dorsal root reflexes" will occur in so few fibers that they cannot have any great functional significance. They (2) studied further the dorsal root potentials attending reflex discharges and found a slow, central negativity concomitant with the response, spreading peripherally by electrotonus. They attribute the dorsal root impulses to this slow negativity and emphasize that increased activity induced by cooling is not confined to the sensory side, but includes also the motor mechanisms. They attribute the action of cooling to an upset in normal synaptic conditions so that two-way conduction obtains, instead of the normal one-way transmission. It is the reviewer's opinion that Barron & Matthews' studies do not belittle the importance of Toennies' observations. Efferent reflex dorsal root discharges may occur in normal conditions (normal temperature), as reported by Toennies. The conclusion that cold disturbs one-way conduction at synapses is not the only interpretation possible of the data. Consequently, two-way synaptic conduction is not proved by these experiments. It is therefore still questionable whether two-way synaptic transmission is possible.

Sensitization of Autonomic Responses

Cannon & Rosenblueth (2) had reported that degeneration of the preganglionic fibers to the superior cervical ganglion results in an increased sensitivity of the ganglion to the stimulating action of acetylcholine. Brücke questioned such ganglionic sensitization and interpreted the results as revealing exclusively an increased sensitivity of the smooth muscle of the nictitating membrane to sympathin. Rosenblueth & Cannon have repeated their original observations and made new ones with adequate controls for peripheral changes. The data indicate that the responsivity of the ganglion to acetylcholine is indeed increased by denervation. Chauchard (2) confirmed this conclusion. The results are in

accord with other observations and have led Cannon & Haimovici to state a general law of sensitization by denervation.

Youmans, Aumann & Haney showed that denervation of the intestine renders it more sensitive to the inhibitory action not only of epinephrine [Luco (1)], but also to that of several other sympathomimetic amines. Simeone & Maes found that sympathetic denervation of the submaxillary gland results in enhanced sensitivity to epinephrine, pilocarpine and, less consistently, to acetylcholine.

Phillips, Hinsey & Hardy found an increased sensitivity of the blood vessels of a sympathectomized foot pad as compared with the normal. These results amend a previous negative report of Hinsey & Phillips.

Tournade & Chardon (2) studied the differences in sensitivity of various normal systems to acetylcholine. The reaction obtained most easily was vasodilation; next came secretion of epinephrine, contraction of the denervated tongue, contraction of the spleen, and respiratory acceleration. Slowing of the heart only took place with much larger doses than those necessary for the other responses.

Danielopolu & Marcu (1) reported that small doses of acetylcholine "sensitize" the vessels to the vasoconstrictor action of epinephrine, whereas large doses of acetylcholine antagonize the responses to epinephrine. It may be pointed out that the term "sensitization" is used loosely in this connection. A small dose of acetylcholine produces relaxation of the vessels. As Phillips, Hinsey & Hardy correctly emphasize, sensitization may not be claimed unless the tests are made from a common baseline [see also Rosenblueth & Simeone (1)]. Danielopolu & Marcu (2, 3) further confirmed Simeone's report that previous injections of epinephrine may lead to augmentation of the responses to subsequent similar injections, i.e., to sensitization. They suggest that epinephrine is transformed after action into a new product which has a sensitizing effect.

Luduena studied the effects of cocaine and pyrogallol on the responses of the retractor penis to epinephrine and to sympathetic nerve stimulation. Pyrogallol increased the magnitude of the responses of the muscle to epinephrine but influenced only the duration of the contraction elicited by stimulation of the sympa-

thetic nerves (cf. Clark & Raventós). Cocaine increased the amplitude and duration of the responses to both modes of activation. A direct action of cocaine was also revealed by the shortening of chronically denervated muscles. The latter observation is similar to that reported by Crosby for eye and ear vessels of rabbits.

Other substances found to increase the responses of smooth muscle to epinephrine were the following: colchicine (Busquet); eucaine, as opposed to tropine and tropacocaine, (Carbunescu); hexamethylene-tetramine iodomethylate (Kaswin). With regard to acetylcholine, Hazard & Cheymol observed that its muscarine-like effects are unchanged by calcium ions, whereas the nicotine-like actions are greatly increased.

Homeostasis

McDonough studied the responses of completely sympathectomized dogs to heat, cold, anoxemia, and insulin hypoglycemia. There were no noteworthy differences between normal and operated animals in rise of body temperature or rate of panting in reaction to heat. In a cold environment shivering began sooner and continued at a faster rate in dogs lacking the sympathetic chains; the body temperature dropped slightly more than in the normal animals. The endurance to low oxygen tension (four per cent) was decreased by the operation. The most striking difference from normal was found in a marked hypersensitivity to insulin. The hypoglycemic symptoms occurred more promptly and were more severe in the operated than in the control animals.

Hodes found sympathectomized cats unable to run as rapidly and as long without becoming fatigued as before the operation. A cardiac acceleration took place after exercise or emotion, greater than that caused by removal of vagal inhibition. It is attributed to accelerator fibers in the vagi. A similar explanation was offered by Brouha, Nowak & Dill for a similar acceleration present in sympathectomized dogs, and by Brouha & Nowak for that which takes place in such animals upon injections of atropine. The last work mentioned brings out the interesting fact that the tonic activity of these vagal cardio-accelerator fibers increases gradually after complete sympathectomy, to attain a stable maximum in about twenty days.

Fuzii reported an increase of the leucocyte count in sympathectomized dogs following muscular exercise and excitement;

this increase was less, however, than in the control animals; the erythrocyte count was not affected. Brouha, Cannon & Dill found completely sympathectomized dogs, with or without the adrenal medulla, capable of regulating their blood sugar within normal limits during and after exercise, after glucose ingestion, and after epinephrine injections. Sympathectomized dogs remained sensitive to insulin indefinitely; this hypersensitivity was dependent merely on denervation of the adrenal glands, for dogs deprived of the adrenal medulla were as sensitive to insulin as totally sympathectomized animals. Edwards, Brouha & Johnson found that increases in blood lactate during exercise were the same in sympathectomized as in normal dogs. The increase in blood lactate following injections of epinephrine was greater in adrenalectomized than in normal dogs and was greatest in totally sympathectomized animals.

A general comparison of completely sympathectomized cats and dogs reveals a much greater deficit in the former than in the latter. This deficit is attributed by Cannon to the presence of accessory functions in the dog, not under sympathetic control.

Hamlin & Gregersen found the plasma volume of sympathectomized cats about twenty-six per cent higher than normal. Both normal and sympathectomized cats showed increases of plasma volume after injections of epinephrine. An increase of plasma volume could explain at least in part the restoration of blood pressure which takes place after complete sympathectomy (B. Cannon). The results of Hamlin & Gregersen, on the other hand, oppose the view that prolonged injections of epinephrine or prolonged hyperactivity of the sympathetic nervous system leads to "shock" (cf. Freeman).

Burton & Taylor observed that the blood flow in fingers fluctuates continually between wide limits. Some of these fluctuations are attributed to rhythmic changes of sympathetic tone. Increase of the environmental temperature slowed the rate of the cyclic changes. The influence of psychic factors was recognized. Masserman studied the action of strychnine on the autonomic pseudaffective responses of cats to hypothalamic stimulation. While intraperitoneal injections did not significantly modify such responses, similar injections into the third ventricle resulted in spontaneous pseudaffective behavior and in an increase of the responses to hypothalamic stimulation. Bender made a further contribution to

his study of the autonomic reactions of monkeys during emotional stress. He confirmed his previous observations, suggesting that acetylcholine is released in relatively large amounts during emotional behavior. A comparison of the reactions of cats and monkeys led him to conclude that while the cat exhibits predominantly sympathetic hyperactivity during emotional stress, the monkey shows mainly parasympathetic hyperactivity in similar conditions.

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THE SPECIAL SENSES

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Of the papers on the special senses appearing from September 1938, to September 1939, an almost undue proportion was concerned with the question of visual purple, dark adaptation and vitamin A. [For a review of this special field for 1938 see Granit (1)]. The direction of advance seems to be toward the multiplication of corroborative detail in favor of theories already proposed. The new departure in the physiology of vision is the growing dissent from the opinion that visual phenomena can be explained wholly, or even in the main, on the basis of photochemical changes in the rods and cones. The feeling exists that other processes, retinal or even central, may be more important for vision than activity in the receptors. This year, as last, work on the ear centers about its electrical responses. An excellent summary of work along this line up to March 1939 is to be found in a review by E. G. Wever (2), one of the two pioneer investigators whose names are indissolubly associated with these phenomena. The physiology of the vestibular labyrinth has been brought up to date in a review by Hyndman (3). Investigators on cutaneous sensations are still worrying over the individuality of these sensations, otherwise this field is not very active. Nor is much work being done on taste and smell. Finally it is to be remarked that there has been an unusually large number of attempts to localize centers in the brain associated with the various special senses, the usual method of extirpation of parts being followed, often after the establishment of conditioned reflexes.

The Eye

Wink reflex and eye movements.—The wink has long been used as the perfect example of a mammalian reflex. Its chronaxie in man, as determined several years ago by Bourguignon (4), lies between 0.48 and 0.72 msec., for the rabbit it is now (5) found to lie between 0.3 and 0.9 msec., with 0.6 as the average. It is claimed that chronaximetric measurements may be useful for studying the effect of drugs such as novocain, cocaine and epinephrine instilled

into the eye. Like other typical mammalian reflexes, the wink has been used in the establishment of conditioned reflexes to light, sound and other stimuli. If, however, the cutaneous area, stimulation of which normally causes a wink, is anesthetized with stovain, the conditioning stimuli are now ineffective, i.e., the reflexogenous area of the unconditioned reflex arc must remain intact in order for the conditioned reflex to be carried out (6). This is reminiscent of earlier experiments on the effect on conditioned reflexes of removal of unconditioned pathways (7).

A clear account of the physiology of ocular movements is to be found in the first lecture of a course by Bielschowsky (8); the remainder of the series on anomalies is of more interest to practicing ophthalmologists than to physiologists. Psychologists are still concerned with methods of registration of eye movements. Of the two methods now in vogue, viz. photographing reflections from the cornea and recording changes in potential through electrodes on the skin, the latter is claimed to have the advantage in that it is quantitatively reliable, the head does not have to be fixed, and the procedure can be carried out in the dark (9). Under different anesthetics the degree of eye movement is markedly different, i.e., with brain-stem anesthetics, such as the barbiturates, the eyes may turn in as much as 35° and out 30°, whereas with ether, chloroform, etc. the range is 8.5° to 7.5°. Stimulation and extirpation of higher levels of the brain, e.g., the appropriate areas in the cerebral cortex, have less effect on eye rotation than lower levels, e.g., the diencephalon and acoustic nerve (10). Thus nystagmus caused by rotating about a cat a drum painted with alternate stripes of black and white persists after hemidecortication and extirpation of the occipital lobes, while injury to the anterior corpus quadrigeminum impairs movements in the eye on the opposite side (11). The anterior cortical ocular centers act independently to maintain the eyeballs in a position of attention, particularly when they are turned to one side; one posterior center can inhibit the other, but both are dominated by the anterior centers (12). Accommodation for near vision and convergence are associated reflexes. An attempt has been made to determine by means of a haploscope the limits within which each reflex can act independently of the other. Near accommodation without convergence at a fixation distance of 40 cm. can be changed from 4.75 D to 0.75 D by interposition of spherical lenses, but convergence cannot be

changed by interposition of prisms without slightly changing accommodation (13). Incidence of exophthalmos, experimentally produced in the guinea-pig by injection of anterior pituitary extract after thyroidectomy, is reduced from 86% to 52% by administration of thyroxin, but not by sodium iodide. Thyroxin is thought to act directly on the orbital structures causing them to lose weight (14).

Pupil.—The relation of the size of the human pupil to fixed brightnesses was worked out by Reeves (15) twenty years ago. Similar measurements have now been made on the cat (16), the pupil varying not only in size but in shape under different states of illumination. The total range of change in the horizontal diameter is from 2 to 14 mm. The pupil is circular and of constant size between the absolute threshold and 0.01 millilamberts; from 0.01 to 100 millilamberts occurs the maximal change.

The pupil has long been known as a sensitive index to responses to stimuli other than light. The delicacy of this index is shown by the fact that it is an even better detector of thresholds of sounds of different pitches than the conscious perception of the sound by the subject. The trained observer is able to perceive dilatation of the subject's pupil when the intensity of the sound reaches the threshold value. Such audiograms have the added value of being objectively rather than subjectively obtained (17). Dilatation of the pupil in response to pain was originally attributed by Karplus & Kreidl (18) to inhibition of the parasympathetic rather than excitation of the sympathetic. Proof for this assumption is now afforded (19). Oxygen lack raises the threshold for reflex pupil dilatation through stimulation of the sciatic in a rabbit under urethane, an effect which is neutralized by addition of 4 to 5% carbon dioxide. This occurs in the sympathectomized as well as in the normal eye. Likewise in the homatropinized eye, stimulation of the sympathetic or of the sciatic produces no further dilatation, though further dilatation occurs on the addition of epinephrine and cocaine. Under deep narcosis, and therefore in absence of pain, very slow dilatation occurs on sciatic stimulation—this is attributed to humoral excitation. Evidently pleasure as well as pain can cause dilatation of the pupil since it occurs in cats from birth and in dogs after three months when they ingest food they like. It evidently becomes a conditioned reflex in dogs since it eventually happens that merely showing them food causes the pupils to

dilate. Fear checks the reaction (20). Mathematical treatment by Elsberg & Spotnitz (21, 22) of data relating area, intensity of light and size of the pupil, shows that cube roots, or some multiple of them, such as ninth and twenty-seventh, are involved. This falls into line with other observations of these investigators on smell and taste, who believe that cube root relationships denote functioning of volumes rather than surfaces. This is interpreted to mean involvement of whole cells, probably in the central nervous system, and not movement of ions along surfaces of axons.

The isolated iris, if relaxed, shows an irregular spontaneous rhythm which is enhanced by weak loading. Mechanical stimuli are therefore effective on iris musculature. Under these circumstances the sphincter and dilator fibers do not oppose each other, as they do with the iris *in situ*, but they cooperate, the total power of the dilator for doing work being greater than that of the sphincter. Parasympathomimetic drugs, e.g., acetylcholine, act on the sphincter and do not affect the relaxed dilator, whereas sympathomimetic drugs, e.g., epinephrine, act on dilator fibers. Atropine causes relaxation of the sphincter and of the dilator as well when the latter is under the influence of epinephrine, i.e., when contracted (23). The only pupillomotor center to be found in the brain is that previously described by Ranson in the postero-medial part of the diencephalon. Excitation of one posterior corpus quadrigeminum causes bilateral mydriasis which is suppressed by section between the anterior and posterior corpora. Mere section between the anterior and posterior corpora has no effect on pupil diameter (12).

Lens.—Work on the lens, as last year, centers about the question of cataract. The most complete list of chemical constituents of the lens yet published is to be found in an article by Krause (24) on the chemical pathogenesis of cataract, together with a scheme to show the possible course of carbohydrate metabolism in the lens from glucose to lactic acid. Krause also summarizes the causes of cataract: the initial effect of mechanical injury is probably precipitation of proteins; of heat, effect on enzyme action; of naphthalene, removal of cystine; of diabetes, increase in organic acids. The presence of silicate in unpurified salt, together with ultraviolet light, is claimed as a factor causing prevalence of cataract in certain districts in India (25). In senile cataracts there is distinct loss in protein; since it is the soluble crystallines which disappear,

the soluble albumins are left and impart to the nucleus an increased rigidity and hardness (26). In naphthalene-poisoned lenses the sugar content decreases, not as a consequence of there being less glucose in the aqueous humor, but because of a disturbance in intermediary products. Organic phosphorus is diminished, inorganic phosphorus increased. It is chiefly the relations between glucose, glutathione and ascorbic acid which are disturbed (27). Cataracts produced by high galactose diet have been compared histologically with those produced by naphthalene and with senile cataracts. In general, the earliest changes occur in the cortical fibers near the equator, the capsule suffers simultaneously or shortly afterwards, the nucleus considerably later (28). On diets lacking riboflavin only two out of twenty-three rats developed cataracts, but when the missing factor was supplied the cataracts were not prevented from proceeding to maturity or appearing in the other eye (29). It has even been shown that certain strains of rats on normal diets develop cataracts spontaneously, together with degeneration of the retina, and that this trait is a Mendelian recessive (30). The responsibility of dinitrophenol for appearance of cataracts in patients taking this drug for obesity has again been denied by Tainter (31), who finds that it has no effect on the rate of appearance of cataract in rats on a high lactose diet.

Normal lenses have a good buffering system (32) and contain the necessary enzymatic components for glycolysis (33), but the respiratory system seems to be imperfect (33). The functions of glutathione in the normal lens are, however, clearly shown to be concerned with the auto-oxidation system in which sulfhydril can act as hydrogen-donor, and when oxidized to disulfide can act as hydrogen-acceptor. The glutathione content of the rat lens at birth approximates that of the blood, rises sharply for a few days, continues to rise slowly until the fourth month, then declines. The major change is in the cortex; in the nucleus there is no marked change. Galactose diminishes the glutathione content of the lens, the effect being again on the cortex. Cataracts so produced disappear on restoration of a normal diet (34). Vitamin B_1 is present in the lens almost exclusively as cocarboxylase, and, if such a distinction can be made, serves as an enzyme rather than a vitamin. It is concerned with the production of pyruvic acid, accumulation of which leads to opacity, this fact explaining the paucity of lactic acid in cataractous lenses (35).

Ocular fluids.—Details of the chemistry of ocular fluids may be found in the following references (36, 37, 38). Of particular interest is the claim that the change of creatine to creatinine is associated in the carbohydrate cycle with the coupling of dextrose to phosphate as the first stage in the glycolysis of glucose. The sclera and vitreous humor have little creatine, therefore a low metabolic rate; the cornea has a higher one (37). All the arguments for the hypothesis that formation of aqueous humor is a secretory process rather than simple dialysis have been summed up by Robertson (39), confirming the stand taken last year by the reviewer. A theory has been offered to explain the mechanism of secretion based upon the assumption of a barrier of selective permeability between the stroma and the epithelium of the ciliary body favoring passage of acid rather than of basic dyes. Such a barrier would be capable of reversible oxidation and reduction, oxidation by the epithelium, reduction by the stroma. The irreciprocal permeability would depend on water and cations being carried from stroma to epithelium, and anions from epithelium to stroma, the energy being supplied by the oxidation-reduction system (40).

The aqueous humor is a favorite medium in which to demonstrate the possibilities of the humoral transmission theory. Rabbits' eyes, however, seem not to work so well for the purpose as those of cats and monkeys. Acetylcholine is released in eserinized eyes on reflex stimulation of the parasympathetic system (41). Even pupillary responses may be used to demonstrate acetylcholine and sympathin effects (42).

Retina.—The position of the retinal blood vessels makes it possible to photograph them by means of a special lighting arrangement. When so examined the effects on these vessels of application of drugs were found not to be wholly consistent, perhaps because the animals (dogs) were kept under deep anesthesia. Epinephrine caused dilatation of the artery in two out of sixteen cases, of the vein in seven cases. Nitrites gave no results. An acetylcholine derivative, one hundred times as potent as acetylcholine, caused constriction in eleven out of twenty trials, dilatation in one (43). Section of the posterior ciliary arteries in the rabbit caused pigmented retinal degeneration (44). Diabetic retinitis is considered to be due to reduction of the ascorbic acid in the blood, not to other changes in blood chemistry (45). The phenomenon of

pigment migration, which is a feature of the frog's eye, has suggested the presence of retinomotor fibers in the optic nerve. Strychnine causes the pigment of the dark adapted eye to occupy the light position; naphthalene causes that of the light adapted eye to assume the dark position. After cutting the optic nerve, application of drugs has no effect. The explanation given for these results is that the central nervous system is the regulator of pigment migration and thus lends support to the retinomotor theory (46).

The changes undergone in the bleaching of visual purple are, according to Lythgoe (47), first, the production of "transient orange," a substance little affected by changes in hydrogen ion concentration, whose absorption is equal to that of the parent visual purple at 470 to 480 mμ; second, the unstable "transient orange" is converted through "indicator yellow" to colorless components. Chase & Smith (48), in their studies on regeneration of visual purple, find that maximum regeneration occurs at pH 6.7 and that temperature has no effect. Zewi (49) in Granit's laboratory also finds temperature has no influence on the process, though oxygen is necessary. Chase & Smith conclude that the process involves only a single reaction and, although dark adaptation data indicate that two molecules are involved, their data show that the reaction is a monomolecular one. The explanation may be that one substance is in very considerable excess of the other. Zewi finds that lactoflavin has no effect on the course of regeneration of visual purple, nor has glucose, although it had previously been found in that laboratory that glucose increases the electrical response during dark adaptation of previously light-adapted excised and opened frog's eyes (50).

The employment of dark adaptation measurements for determining vitamin A deficiency has given rise to an extraordinary number of methods and instruments for this purpose (51 to 62). A critical review of methods is given by Sloan (51). Some of the newer methods take advantage of the human infant's pronounced positive phototropism (52); others differ from the usual run by employing binocular matching of test patches (53), and some are directed toward adaptation of the fovea alone (54). Even the rat can be examined by means of conditioned reflexes in which the animals are given shocks if they press levers beneath dark panels, food if they choose a light panel (55). Although a rapid test, such

as looking at a bright light for thirty seconds, then finding the time necessary to see a dim light of constant intensity (56) may give results which are statistically significant for whole populations most of the dark adaptation curves obtained for the individual are, according to Tansley (57), worthless since they ignore pupil size, may have been taken from the fovea where there are no rods, and are often carried out only for ten minutes in spite of the fact that it is the latter part of a thirty minute curve which is most affected by lack of vitamin A. For precise measurements a constant, i.e., artificial pupil must be employed (58, 59) since a large pupil in the dark tends to decrease perception time; also in old age there is a significant decrease in pupil diameter both in the light and in the dark and a slowing of the rate of dark adaptation as well. Lowered oxygen tension, as at a simulated height of 7,400 ft., elevates for many individuals the dark adaptation curve in both the cone and rod parts, but especially in the latter; at 15,000 ft. all persons tested were so affected. All were restored to normal by proper oxygen tension. This prompts the suggestion that here the results are due not to failure of action on the part of the photochemical substances in the retina, but rather of the neural elements of both retina and central nervous system (63).

Granit's (1, 64, 65, 66) attempts to correlate action potentials with the chemical phenomena occurring during visual purple bleaching and resynthesis make him believe that there is need for drastic revision of our current ideas. He has shown that after moderate light adaptation, the electrical response of thoroughly dark adapted eyes may be reduced, although there is no measurable reduction in visual purple concentration. He finds that the greater part of the visual purple bleached is useless for stimulation, and assumes that it is only the small fraction on the surface film of the rods which, upon bleaching, furnishes the necessary stimulus for setting off the nerve impulse. The main store of visual purple is inside the rods and that on the surface can be renewed by diffusion from this inner store. The rods may thus be forced to nearly maximal activity without incurring measurable losses in visual purple content. Granit states that there must be an intermediary process between visual purple regeneration and rise in retinal sensitivity, because he finds that the latter process occurs at a distinct interval after the former. This can only mean that the rise in sensitivity during dark adaptation is not a simple function of

the curve showing the course of visual purple regeneration. The spectral distribution curve of the bleaching of visual purple coincides with neither rod nor cone spectrum (frog's eye), nor is it to be explained as the sum of these two spectra superimposed. In a word, in his opinion, regeneration of visual purple is of little immediate significance in the actual process of excitation of the rods by light. It remains to be seen how this challenge will be received. Elsberg (67), on other grounds, believes that photochemical processes cannot alone be responsible for the phenomena of dark adaptation.

In the face of utter lack of correlation between diet and dark adaptation curves obtained in certain English hospitals (68), Wald's experiment on human vitamin A deficiency of last year has been repeated (69, 70) with results similar to those of last year, the point being that on the thirty-fifth day when the minimum threshold for cones was 3.4 times the normal, and that for the rods 9.1 times the normal; fourteen minutes after administration of carotene the thresholds began to change and in forty-nine minutes had reached their normal level. The results of Hecht & Mandelbaum's (71) human experiment differ from those of Wald in that in that their subject there was no spectacular return to normal in less than an hour, but only a gradual return during the subsequent two months. Wald attributes the difference to the fact that his subject was given a planned diet containing the optimum amounts of other vitamins and minerals. The parallel behavior of rod and cone thresholds leads Hecht & Mandelbaum (72) to postulate photochemical changes in "iodopsin" or "visual violet" in the cones, and they suggest that this substance is a conjugated carotenoid protein like "rhodopsin" or "visual purple." Wald (73) has added another photochemical system to his list; the porphyropsin system in certain fresh water fish; in it porphyropsin breaks down in the light to a retinene and a protein, which when combined with a substance resembling vitamin A restores the porphyropsin.

Ludvigh's criticism, mentioned last year, that scotopic visibility curves should be corrected for selective absorption of light by the different refractive media of the eye has now (74) been applied to standard curves such as those of Hecht, even with Blum's correction. These doubly corrected curves are like those of Lythgoe for the absorption spectrum of visual purple uncor-

rected for yellow impurities, and can be correlated with the heights of the b-wave in Granit's retinograms.

A study of the polarity potential of the human eye, in which, as in the eye of the frog, the cornea appears to be positive and the retina negative, has been begun by Miles (75, 76, 77). At the present stage of the investigation, however, little more has been accomplished than successful registration of the phenomenon. Bartley (78) proposes some slight modifications in Granit's system of reference letters for the action potential from the eye, viz. *a* for the initial negative wave; *b*, the positive; *c*, the long gradual drift; *d*, the "off" effect; PI for the potential developed in the ganglion cells; PII, that in the bipolar cells; and PIII, that in the sensory organs. (Granit associates PII with excitation and PIII with inhibition.) The reason for the change is that asphyxia, ether, calcium and potassium eliminate PII before PIII. Bartley concludes that there is no simple relation between sense cell discharge and the quantitative aspects of ultimate sensation, and that the three types of discharge are the result of reorganization at synapses in the retinal layers. An extensive series of oscillograph records of the activity in the non-anesthetized cat's occipital cortex made by Claes (12) allows us to compare these waves with those from the optic nerve. Asphyxia weakens the "on" and "off" response; light adaptation diminishes Granit's "*B*" wave, has no effect on "*d*," weakens the "on"-effect, reinforces the "off," while dark adaptation does the reverse. This author (12) agrees with Hartline (79) that the "off"-effect (here registered in the cortex) is not post-inhibitory rebound, but the action of special neurons excited by darkness or diminution of light. A continuation of Crescitelli's experiments on the electrical responses of the grasshopper's and moth's eyes (80 to 83) again shows how these responses are related to those Granit findings for the vertebrate eye; the *b*, *c*, and *d* waves are present, *a* is lacking, but at low intensities of white or colored light the *a* wave appears.

Crozier (84 to 88) is continuing his studies on the flicker response. The *raison d'être* of these studies is as follows: the reciprocal of mean critical intensity at fixed flash frequency is taken as a measure of excitability; with increasing temperature the data fall on the curve for the Arrhenius equation to a certain point where a break occurs; such behavior is to be explained on the theory that ease of excitation is governed by temperature through its control

of the velocities of catalysed chemical processes common to all the sensory elements concerned. The inadequacy of the hypothesis that the data of flicker and other visual responses can be interpreted in terms of retinal photochemistry is pointed out [cf. Granit (1), (66)]. Crozier considers that reaction volocity is a more fundamental characteristic of excitability. The method of critical frequency applied to the human eye during dark and light adaptation shows that it decreases during dark adaptation; it increases during light adaptation only up to a certain limit, then decreases. Twenty-four hours after adminstration of strychnine neither light nor dark was found to influence fusion of light flickers, because of lowered synaptic resistance presumably between retinal sense organs and ganglion cells (89). There have been several papers on differential sensitivity of the retina, both recalculations of former data and new determinations. Piéron (90) reiterates his statement that thresholds for brief durations of light stimuli, particularly at the lower limit, present anomalies. Crozier (91) has compared the threshold stimulus intensities in the human eye along the 0° to 180° meridians with Østerberg's counts of retinal elements and finds no direct correlation between visual sensitivity and the number of retinal elements. This is taken as a further argument [see also Holway & Hurvich (92), and Stiles (93)] that quantitative properties of visual data are not directly determined by the properties of the peripheral retina, as assumed by Hecht (94) [see also Graham *et al.* (94, 96)].

It has been suggested that visual acuity is limited by chromatic aberration and diffraction. With the grating test, maximal visual acuity is progressively lowered in light of wave lengths longer than the orange, provided the pupil is about 2.3 mm. in diameter. A pupil 3 mm. in diameter gives maximal values. With the "C" test, maximal visual acuity with a pupillary diameter of 2 and 3 mm. in monochromatic light from different parts of the spectrum remains unchanged. These findings are inconsistent with the above suggestion (97). Central visual acuity is found to be unchanged by oxygen deprivation up to the equivalent elevation of 23,000 ft. The visual field, however, is narrowed to a region 8° to 10° about the macula (98). Visual acuity is, of course, a most important requirement for automobile drivers and fliers, and tests should be reliable (99). Of importance for night flying are the ability to see scotopically, viz. the flier's threshold, amount of dark adaptation,

but still more his speed of dark adaptation (100). Visual acuity is likewise unaffected by injection of morphine or codeine, although they produce myosis. Cobra venom, on the other hand, improves visual acuity (101). It is interesting to note that the visual acuity of the pigeon for wave lengths between 711 and 460 mμ is about the same as that of man. Its visual acuity is poorer at 30 cm. distance than at greater distances. This bird's hue discrimination is also about the same as man's. In this bird accommodation occurs very rapidly and there is reason to believe that corneal curvature and the position of the lens are involved as well as changes in curvature of the lens (102). In both rats (103) and dogs (104) it has been shown that there is still light discrimination after extirpation of the occipital lobes of the cerebral hemispheres. Subcortical regions therefore must possess light discriminatory powers.

For the details of the studies on stereoscopic localization in which the data are supplied by disparities between retinal images in the two eyes caused by slightly different points of view, the reader is referred to the original articles by Ogle (105, 106) on "the induced size effect," and also to that of Kompaneiski (107). A discussion of binocular vision in domestic animals, horse, cow, dog, guinea-pig and rabbit will be found in an article by Píša (108).

The greater part of the recent work on color sense deals with psychological rather than with purely physiological aspects of the subject. The warning of Boring (109), however, is applicable to both psychologists and physiologists that "just noticeable difference" is not as good a measure of color differences as is the "differential limen." The latter is defined as "the stimulus value for a difference which occurs with a given frequency." Even it is not entirely satisfactory, since it is a measure of the readiness of an observer to use the "equal category" in making judgments and this cannot be accurately controlled. In Boring's opinion one should judge on the basis of "greater" or "less" but not "equal." The normal eye distinguishes four "primary" sensations, only three of which are on the spectrum: yellow (570 mμ), green (560 mμ) and blue (470 mμ). Primary red is a mixture of spectral red and violet (or blue) which, however, can be located accurately spectroscopically under proper conditions, e.g., after two and a half minutes in the dark (10). This particular "unique" red completes the list of seven psychologically unique colors, and any color can be described by the following equation: x(red or green)

$\pm y$(yellow or blue) $\pm z$(black or white) $+ g$(gray) = the color in question (111). One of the recent color theories is based on piezo-electric resonance in the rods and cones (112) [cf. Stevens & Davis (113), chapters 13 and 14 on piezo-electricity in the cochlea]. Another relates color vision to cerebral cortical activity since through hypnosis persons with perfectly normal color sense can become red, green or red-green color blind (114).

The Ear

In spite of the immense amount of research initiated by the discovery of the Wever-Bray phenomenon a decade ago, the interpretation of electrical responses from the ear still divides investigators in this field into two main camps, adherents of the place theory, and those who favor the resonance theory. The case for the place theory has been again set forth by Jeffress (115) [reviewed also by Stevens & Davis (113)] who concludes that the evidence for it is quite adequate. Delicate experiments on the detachment of short lengths of the spiral ligament of the spiral organ (of Corti) from the bone, however, show that tonal localization in the cochlea is less sharp than usually assumed, although the localization for high pitches is much more exact than for low ones (116). Likewise, rhythmic condenser discharges arranged for bone conduction give rise to waves of such modified form that it is concluded that the central nervous system as well as the spiral organ must play a role in the ultimate determination of pitch (117). Wever & Bray (2) still advocate their resonance-volley theory which combines the fundamental features of the traditional place and frequency theories.

The question of the origin of cochlear potentials—whether they arise from the activity of hair cells of the spiral organ, or are developed by movement of liquids across the vestibular (Reissner's) membrane as a result of chemical differences between endolymph and perilymph—is also still unsettled [cf. Stevens & Davis (113)]. Evidence in favor of the former locus is given by Walzl (118) who finds that crystals of sodium chloride and potassium chloride applied at the basal coil of the cochlea impairs the electrical response to high tones, at the apex to low tones. If the perilymph is replaced by isotonic solutions, of such salts as sodium and potassium chlorides, there is impairment for all tones equally. From these data the conclusion is drawn that the effect of the salt

crystals is due to chemical action and not to osmotic changes. This rules out the possibility of the cochlear potentials being due to streaming or concentration potentials across membranes separating the perilymph from endolymph. The view that the magnitude of microphonic potentials is a measure of sensitivity of the auditory organ is challenged by Pumphrey (119) who obtains like potentials from the labyrinth of a fish to air-borne sounds and vibrations transmitted through solid and liquid media. They come from the sacculus and utriculus. His challenge is based on von Frisch's statement that the utriculus plays no part in hearing in fish. If this were true, then the generation of such potentials would not be sufficient indication of the reception of acoustic stimuli.

Hearing by bone conduction has recently been investigated in connection with hearing aids for the deaf, the object being to establish norms (120, 121). A proposed standard for loudness is considered by Brittain (122) and difficulties due to fluctuation are dealt with by Lifshitz (123). Reception of air-borne vibrations begins, of course, in the external auditory meatus. The physical aspects of resonance in this organ can be studied by replacing the air by hydrogen (124). Audition produced by electrical stimulation of the ear is not the result of an effect on the inner ear as one might suppose, but upon the ear drum. The drum is moved by electrostatic pressure whenever a difference of potential is established between the tympanum and the opposite wall of the middle ear (125). The degree of patency of the auditory (Eustachian) tube plays a part in the distinctness with which sounds are heard. By manometer measurements it can be shown that the tube offers a resistance of 20 mm. Hg when the subject is in the erect position; it is increased in the prone position and upon flexing the head toward the chest; decreased by exercise and on swallowing; 60 mm. Hg is compatible with normal auditory function. Below 20 mm. Hg crackling sounds are heard. If the tube remains continuously open, direct transmission of sound from voice and breathing masks hearing for all sounds near their threshold (126).

After establishing conditioned reflexes to sound, extirpation of one temporal lobe of the cortex, or transection of the corpus callosum does not extinguish the reflex (127). Conditioned reflex experiments also show that the medial geniculate body is a projection of the spiral organ (of Corti) in the sense that response to 8000 cycles per sec. occurs in the dorsal part, to 4000 cycles per

sec. in the anterior part, to 2000 cycles per sec. in the lateral part, to 1000 cycles per sec. in the posterior part, to 500 cycles per sec. and below in the central parts of the geniculate body. This is taken as evidence in favor of the place theory (128). Cobra venom produces a similar effect on the ear to that on the eye; it increases acuity of hearing by 4 to 10 decibels; morphine decreases it by 4 to 20 decibels (129).

The relation of the vitamin B complex to deafness is by no means clear-cut (130). Lack of vitamin A, however, produces in young animals degeneration of the cochlear nerve and the spiral ganglion. It also causes serous labyrinthitis involving both the spiral organ (of Corti) and the semicircular canals. The vestibular nerve is affected but to a less degree. The effects are due to an overgrowth of bone at the base of the skull which presses on and stretches the nerves in this region (131).

The binaural ability to locate the source of a sound is said to be dependent upon two factors: time difference and intensity difference in the two ears. Binaural cues are effective only in determining the angle between the direction of the sound and the axis of the ears, i.e., the lateral angle. Localization in the median plane is determined by head movements. Here the value of the lateral angle should so change that a sequence of lateral angles must characterize the direction of the sound geometrically in both directions. This has been shown to be the case by the observer's perceiving a sound whose source was shifted horizontally as if it were coming in the direction from which the presented sequence of lateral angles was derived rather than in the direction from which the sound was actually coming (132, 133).

Among the motor reactions to sounds the "startle" pattern has now emerged as an entity: the eyes are shut, the features distorted, shoulders drawn forward, etc. It is present in all normal persons including infants and is even present in those deaf who cannot hear speech distinctly, but is not present in certain epileptic and psychotic patients (134).

The sense of hearing in amphibians has been discussed by Ferhat-Akat (135), and that of birds by Knecht (136).

The Labyrinth

Destruction of parts of the labyrinth has been practiced for so many years that one would think the possibility of new observa-

tions had long since ceased. Yet it has only recently been shown that the mammal differs from the lower vertebrates in that its semicircular canals can be stimulated by movement in either direction. Nevertheless each canal is more easily excited by rotation in one direction; the horizontal and posterior vertical respond best to ampullopetal movement, the anterior vertical to ampullofugal. This latter effect is contrary to Ewald's rule. Rotation nystagmus is a true reflex effect, ceasing when both labyrinths are removed (137). In the pigeon a lesion of one labyrinth produces head bending after twelve hours, but after a month there is complete compensation through the vestibular center in the medulla (138). Since much of our knowledge of vestibular function is based upon models, the reader's attention is called to a description of a new model constructed by Steinhausen (139). It has long been known that the passage of a current through the head causes "galvanic" falling and past-pointing. Since the current must be galvanic (not faradic), since the direction of the fall is related to the direction of the current, and since a stimulus of 0.000033 sec. duration is sufficient, it is concluded that the effect is not the result of direct stimulation of the vestibular nerve, but is due to electrokinesis of the endolymph (140). This same reaction has been studied in normal (141) and labyrinthectomized (142) guinea-pigs. The majority of normal animals fall towards the anode, away from the cathode, but about a quarter do the opposite. After unilateral labyrinthectomy these proportions are reversed, i.e., about three times as many are predisposed to reactions in the opposite direction. Some reaction was obtained even after bilateral labyrinthectomy. Conditioned reflexes can be established in dogs for position and uniform motion in different directions which persist when semicircular canals, dorsal columns and dorsal spinocerebellar tracts are eliminated. When, however, the dogs are conditioned for accelerated motion, after labyrinthectomy discrimination of direction of rotation about a vertical axis at low acceleration is lost (143).

Cutaneous Sensations

The reliability of mapping the skin in successive trials for cold-spots (144) is greater than for warm-spots (145). The distribution of cold-spots is uneven; there are peaks of sensitivity where their density is greatest and valleys where they are absent.

Adaptation and vascular changes interfere with mapping of warm-spots. The theory that the cutaneous sensation of heat is dependent upon simultaneous stimulation of hot- and cold-spots is untenable (146, 147), since a sensation of heat may be aroused when the nearest cold-spot is at least two millimeters away. Zotterman (148) has now elaborated his thesis mentioned last year that sensations of touch, pain and tickling are mediated over different nerve fibers, as shown by the difference in character of electrical responses of the cat's saphenous nerve to stroking the skin, burning and pricking with a needle. A study of electrical discharges from cutaneous nerves of the frog shows that when the skin is stretched the rate of adaptation is rapid, as it is for touch and pressure. Lowered calcium in the skin increases the duration of the discharge (149). Piéron & Segal (150) report a peculiar effect of subthreshold condenser stimuli on the digital branch of the median nerve in man. If a subthreshold stimulus is followed at an interval of more than 0.1 sec. by a shock above threshold value, not only is the second felt, but the first as well. This is explained on assumption of sufficiently long delay paths, so that the second shock coming between direct and retarded volleys is supposed to make the subthreshold volley effective. The phenomenon is termed "retroactive facilitation." Another peculiar tactile reaction is described by Schaeffer (151) who states that, in contrast to the discrete sensations aroused by the usual punctiform method of examination, a shower acting on a restricted part of the body gives rise to an apparent movement in spirals and to-and-fro surges. He compares this sensation of movement to Helmholtz' old observation that as one looks at a relatively isolated dim star, it appears to drift in the visual field. For nearly half a century the question has been debated whether pain is a sensation *sui generis*, or merely the result of any intense stimulation. Dallenbach (152) has reviewed the whole evidence and concludes that pain is a separate sense. If it is a separate sense, it should adapt without change in quality, which he finds it does. A convenient method of determining an exact threshold for pain is to find the number of calories per second per square centimeter from a 1000-watt bulb which will arouse a sensation of pain on the forehead. The threshold, as measured under these circumstances, is found to be constant for months. Acetylsalicylic acid, morphine and codeine raise the threshold to pain but not to heat (153, 154). It is suggested that the chemical

mediator for pain is histamine (155), since injection of thymoxyethyl diethylamine, which is a specific against histamine, abolishes pain to pricking, pinching, etc.

Taste and Smell

Of the methods employed in determining the threshold for taste, viz. placing a drop on the tongue, taking ten cubic centimeters of fluid into the mouth, comparing a solution with distilled water, and sampling two solutions as often as desired, the last is the most useful and can be applied to animals. Man can distinguish a 0.01% solution of sodium chloride from distilled water, but to recognize the salty taste the concentration must be about 0.07% (156). Formulae relating stimulus, reaction time and diameter of area stimulated have been constructed for taste as for vision, olfaction, hearing and the reaction of the pupil to light, by Elsberg (157) [cf. (158)]. These formulae involve cube roots or multiples of cube roots (67) as mentioned previously in this review. Action potentials from the cat's gustatory nerves in response to sodium chloride, hydrochloric acid, quinine and sucrose on the tongue show that the receptors respond specifically to certain of the four types of stimuli, and that the same organs adapt slowly. The potentials for taste are smaller than for touch and pressure (159).

Elsberg (160) has outlined more fully his method of localization of tumors by olfactory tests mentioned last year. After the establishment of conditioned reflexes in dogs to the odor of cloves and asafetida, removal of the parietal, occipital and temporal lobes of the cerebral hemispheres, exclusive of the pyriform and hippocampal areas, has no effect on the conditioned reflexes, except that removal of the motor cortex somewhat delays their acquisition (161). In the fish electrical potentials are obtained from the olfactory nerve upon application of both mechanical and chemical stimuli. The latency is 0.5 to 5 sec.; adaptation is neither particularly fast nor slow. There is a refractory period lasting 5 to 20 sec. After application of aniseed there is an "off"-effect (as in the eye) while it is being washed away with water (162).

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ENDOCRINE GLANDS

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In one brief chapter, it is obviously impossible to mention, far more to discuss, all the papers published in a single year which make significant contributions to our knowledge of the hormones. We did not feel justified in omitting from consideration the glands which were fully dealt with in the last volume of these reviews, since they continue to attract a great deal of attention; on the other hand, we did not wish to omit, for yet another year, all mention of other endocrine organs. Accordingly we have made no attempt to cover the whole literature for even one single hormone but have preferred to select isolated topics out of the whole field, which in our opinion especially merited discussion at this time.

Androgens

The metabolism of androgens has been studied with interesting results. Kochakian (1) recovered androgenic material from the urine of castrated dogs only when large amounts (120 mg. or more) of testosterone derivatives were administered subcutaneously, and only in traces at best. But with the increasing employment of testosterone propionate in large doses in the treatment of male hypogonadism, opportunities for more complete study became available. Dorfman & Hamilton (2) found that 20 mg. of testosterone propionate injected intramuscularly daily seemed therapeutically adequate in a case of hypogonadism, and restored to normal the deficient excretion of androgens; if the excreted androgen was androsterone, some forty per cent of the administered hormone was accounted for. Similar results with recoveries of the same order were obtained in four eunuchoids (3) and also in a large series of cases less fully described (4), where it was found that normal males also showed increased androgen excretion during testosterone treatment, followed by a decreased excretion which may have indicated a temporary depression of pituitary activity. Women treated with testosterone also show increased androgen excretion (5). Cook *et al.* (6) actually isolated androsterone from the urine of one of the above-mentioned subjects. At the same time, Callow (7), using a carefully elaborated technique (8),

isolated from the urine of another subject treated with testosterone propionate small but approximately equal amounts of the inactive aetiocholan-3-α-ol-17-one and of the corresponding *allo* compound, androsterone. These compounds were also recovered in other cases (9) and were found in still smaller but parallel amounts in the urine of normal men and women (10). Thus the origin of androsterone from testosterone, so long assumed, may be regarded as established, though other modes of formation are not excluded; further, the transformations of testosterone in the body are fully analogous to the conversion of progesterone into pregnandiol and *allo*-pregnandiol. But as the 3-β compound, dehydro-*iso*-androsterone, was not excreted in increased quantities in these cases, while it appears in large quantities in the presence of adrenal tumor (11), it seems reasonable to regard it as a product of the metabolism of adrenal cortical steroids (12). All three of these urinary steroids are excreted by ovariectomized women (13).

If one assumes that, in the studies already discussed (2, 3, 4), the androgen excreted was androsterone, and that it was accompanied by equal quantities of its inert isomer, then a large part of the injected testosterone is accounted for. But it is important to note that the discovery (14) that testosterone injections also cause excretion of phenolic estrogens has been confirmed in several male patients some of whom were castrated (3, 15, 16), though it was not observed in women (17), or in dogs (18). Immature male and female monkeys treated with testosterone propionate excreted androgens, and probably estrogens also (19); rabbits similarly treated also excrete androgens, especially after thyroidectomy, which may retard hydrolysis of the ester (20).

A great many papers have been devoted to the action of testosterone propionate and other androgens upon the female organism; but as the subject has been recently reviewed (21, 22) we exclude it from discussion.

Ovarian Hormones

Much important recent work in this field is discussed in the chapter on reproduction in this volume. We may note here that an important point has been finally established: adequate doses of pure progesterone (2 to 4 mg. daily) will permit pregnancy to continue to term in the ovariectomized rabbit (23, 24). Estrogens will maintain pregnancy in the hypophysectomized rabbit (25),

presumably because they maintain the activity of the corpora lutea; this is also the probable explanation of the effect of estrogens in delaying parturition (26). Though there have been some dissentient voices, a large number of workers have satisfied themselves that progesterone has power to maintain adrenalectomized animals (27 to 32). Similarly, it has been found that desoxycorticosterone promotes the progestational reactions (33, 34, 35, 36).

The discovery that estrone is excreted in the urine of pregnant women and mares in the form of a sulphuric acid ester (37) is confirmed (38). Human pregnancy urine also contains, in conjugated form, a non-ketonic estrogen (39) identified as estradiol (40).

Adrenal Glands

Harrison & Darrow (41) have greatly clarified our understanding of adrenal insufficiency. The normal dog can, at need, conserve sodium or chloride, and excrete almost sodium free urine; and when the plasma potassium is raised by injection of potassium salts to seven millimols per liter, the kidneys can concentrate potassium fifty fold or more, and excrete up to eight millimols per hour; even under these circumstances, the creatinine clearance indicates that much potassium is being reabsorbed from the tubules. In adrenal insufficiency, on the other hand, the decrease in plasma sodium does not arrest sodium excretion; in fact, the kidney may still be concentrating sodium at first though the decline of inulin and creatinine and urea clearances later indicates diminished glomerular filtration (which is also observed in other forms of sodium depletion); urine flow is not much reduced, however, and losses of sodium continue. On the other hand, despite the rise in plasma potassium, the kidney has lost much of its power to concentrate potassium and phosphate, and their excretion is slow. The administration of large amounts of solutions containing both sodium chloride and bicarbonate promptly, but temporarily, restores plasma sodium levels and improves creatinine and urea clearances while the diuresis sweeps considerable quantities of potassium out of the body. Nevertheless the power to concentrate potassium highly, and to retain sodium, is in no way regained in treatment with salt alone; this capacity is however quickly (if incompletely) restored by treatment with cortical extracts. The total concentration of fixed base in the urine varies comparatively little, and it becomes more evident than ever that the adrenals

are concerned with unknown reactions which differentiate between sodium and potassium. Adrenalectomized rats, injected with the chlorides of radioactive isotopes of sodium and potassium, excreted the "tagged" sodium more rapidly and the potassium more slowly than normal rats (42); but in these experiments it was found that merely allowing the rats to drink one per cent sodium chloride instead of water, after the operation, restored these deranged excretion rates to normal. It was also noted (43) that rats reared on a low sodium diet resemble adrenalectomized rats in excreting radio-sodium rapidly and radio-potassium slowly, while potassium deficient rats tended to retain radio-potassium and excreted radio-sodium normally. Adrenalectomy produces no specific pathological change in the kidney (44), and of course no one would claim that the kidney is the only organ directly affected: cortical extracts still maintain life and prolong the ability to work in rats from which all abdominal viscera have been removed (45). Previous studies on adrenalectomized rats have been extended to cats and dogs, confirming the observation that in insufficiency the skeletal muscle cells take up potassium and water, cardiac muscle some potassium only, while liver and kidney are not affected (46). Marenzi, however, finds in adrenalectomized rats that liver and heart become poorer in potassium, while skeletal muscle and brain maintain constant levels (47, 48); despite the apparent contradictions, it will be noted that the relative behavior of muscle and liver is agreed on.

The theory that the adrenal cortical hormones are specifically concerned with phosphorylation in the intestinal absorption of sugars and fats seems to make little progress. The view that adrenalectomized rats can absorb glucose at a normal rate, if their general condition is maintained by allowing them to drink saline solutions, has been confirmed (49); in such animals, too, the rate of disappearance of corn oil or of methyl esters of fatty acids, from the stomach and intestines remained normal (50), and the rate of entry of fatty acids ("tagged" by formation of conjugated double bonds, which renders them spectroscopically recognizable owing to their high light absorption coefficient) into the phospholipids of the intestinal wall was also normal (51), though greatly decreased by iodoacetic acid. The absorption of sodium and of chloride was found to be somewhat slow, and it was suggested that adrenal insufficiency affects animal membranes in

general rather than a specific chemical reaction such as phosphorylation (52). In Verzár's laboratory, however, adrenalectomized or hypophysectomized frogs are found (53) to lose the power to adsorb glucose and galactose more rapidly than other sugars.

Secker (54) found that while in normal cats stimulation of pre- or post-ganglionic cervical sympathetic fibres elicited contraction of the nictitating membranes time after time without apparent fatigue, when the same experiment was attempted immediately after adrenalectomy the response soon decreased and eventually vanished. Yet an injection of epinephrine still evoked a normal contraction, and even produced partial and very transient recovery of the response to nerve stimulation (probably because subthreshold amounts of the epinephrine persist around the myoneural junction and co-operate with subthreshold amounts of the humoral transmitter liberated at the nerve ending). The injection of adrenal cortical extract ("Eschatin") led, however, within a few minutes to complete recovery of the response to nerve stimulation which was maintained for a considerable time; indeed, the reappearance of the "fatigue" might be slower than its original appearance, though the dose was only 0.1 cc. per kg. A second injection of Eschatin was hardly less effective than the first. This suggests that the cortical extract supplies some non-sympathomimetic factor which either is or controls the formation of some part of the humoral transmitting mechanism. It was noted (55) that each stimulation was accompanied by a slight rise in systemic blood pressure (presumably due to sympathin liberation); this effect declined as the response of the nictitating membrane decreased, but was similarly restored by administration of cortical extract. Perhaps the most surprising point in this report is that the absence of the adrenals should make itself felt so rapidly. Armstrong and others (56) observed that, in the terminal stages of adrenal insufficiency in cats, stimulation of the splanchnic nerves or injection of nicotine had hardly any pressor effect, even when the blood volume was restored to normal with saline; yet epinephrine still had a marked pressor effect. In these experiments powerful and sustained contractions of the nictitating membrane were elicited by stimulation of the cervical sympathetic, even though the animals were moribund. In this connection we may mention the note of Bülbring & Burn, who found that the contractile response to stimulation of the motor roots, in the

perfused hind limb of the dog, gradually failed (while the muscles remained responsive to direct stimulation); the response could be restored by addition of very small amounts of epinephrine or posterior pituitary extract to the circulating blood, while cortical extract was ineffective; the response was not dependent on an increase in perfusion pressure (57).

Gaddum *et al.* have studied the substance liberated when the post-ganglionic fibres running from the superior cervical ganglion to the rabbit's ear are stimulated; these fibres are believed to be purely vasoconstrictor and to have no inhibitory actions. They believe the substance to be epinephrine, because (*a*) it gives a positive test (58) in the arsenomolybdate color reaction of Shaw (59, 60), which in the modification used is highly specific and not given even by such closely related substances as *nor*-epinephrine (arterenol) or adrenalone; (*b*) it has an inhibitory effect on the fowl's rectal caecum (61), which contradicts the theory that there are separate excitatory and inhibitory "sympathins"; (*c*) the colorimetric determination is in quantitative agreement with the action on the frog heart, and on the perfused rabbit's ear, when the assumption is made that the active principle is epinephrine itself (62). It is also suggested (58) that many of the effects of ephedrine (not including its action on the nictitating membrane, for example) depend upon its inhibition of the amine-oxidase which destroys epinephrine, as the action of physostigmin is to inhibit cholinesterase: ephedrine, while without constrictor action of its own in these experiments, increased the response to both epinephrine injection and nerve stimulation, and increased the yield of epinephrine as determined colorimetrically in the perfusate; moreover, the inhibitory action of ephedrine as has been observed *in vitro* (63). Cannon & Lissák (64, 65) find that extracts of tissues rich in "adrenergic" nerve fibres contain a substance pharmacologically indistinguishable from epinephrine (though the effort to exclude related sympathomimetic compounds has not been pushed as far as in Gaddum's studies); but they believe that this epinephrine is modified, perhaps by combination with other local substances which make it predominantly excitatory or inhibitory, before it escapes into the blood as "sympathin."

Posterior Pituitary

The interaction of adrenal cortical and posterior pituitary hormones in water metabolism has been further studied. Corey,

Silvette & Britton (66) maintain their view that these hormones are antagonists. Hypophysectomized rats usually show, in the first twenty-four hours after operation, a transient increase in urine volume but always a marked decrease in the rate of chloride excretion, so that urine chloride concentration is greatly reduced; these changes are not affected by adrenal cortical extract, and are completely corrected or over-corrected by posterior-pituitary extract in doses of five units every four hours. Adrenalectomized rats, immediately after operation, somewhat resemble hypophysectomized rats, but the increase in water excretion and decrease in chloride excretion are far less striking; cortical extract produces definite polyuria and increases the rate of chloride excretion above normal, while posterior lobe extract is antidiuretic and increases urine chloride concentration without much effect on the rate of chloride excretion. Rats simultaneously adrenalectomized and hypophysectomized showed no polyuria, but the rate of chloride excretion was much reduced. The authors are inclined to believe that the decreased chloride excretion that immediately follows adrenalectomy indicates a compensatory decrease in posterior pituitary activity. The effect of "dummy" operations was conscientiously investigated; nevertheless, the significance of the observations is undoubtedly diminished by their proximity to the surgical procedures. The tendency of pitressin to lower blood chlorides has been noted elsewhere (67, 68).

It has previously been shown that cats in which permanent diabetes insipidus has been produced by interruption of the supra-optico-hypophyseal tracts survive adrenalectomy only for a very short time. They become dehydrated very rapidly but the total loss of water at death is not as great as in untreated polyuric cats; moreover, there is no especial tendency towards fatal hypoglycemia (69). Such animals also differ from ordinary adrenalectomized cats in showing little decrease in serum sodium or chloride, though the usual increase in plasma potassium is observed. Pitressin, in doses of three pressor units thrice daily which is sufficient to control the diabetes insipidus, but not enough to affect the fluid exchange of normal cats conspicuously, prolonged the life of these animals considerably and allowed the serum sodium and chloride to fall (70); in short, it masked the diabetes insipidus and allowed the normal sequelae of adrenalectomy to develop. The doses of pitressin used will not affect the concentration of sodium, potassium or chloride in the serum of normal or polyuric cats with

intact adrenals. That inactivation of the posterior pituitary should retard loss of chloride from the serum, as it retards chloride excretion (66), is natural enough; consequently it doubtless aggravates adrenal insufficiency since now to the drain of water from the blood into extracellular tissue spaces, and eventually into intracellular spaces, (46, 47), is added draining-away from the kidney. It is interesting to note that while the cortical hormones act very differently towards sodium and potassium (41), there is so far little to suggest that this is true of the posterior lobe principles.

In the meanwhile the same general problem had been attacked from other angles. The discovery by Gilman & Goodman (72) that dehydrated rats excrete an antidiuretic substance unless they have been hypophysectomized was confirmed (73, 74), and it has been shown more recently that a similar antidiuretic substance is excreted by cats when dehydrated, unless the supraoptico-hypophyseal tracts have been interrupted (75); as these lesions lead to a disappearance of the antidiuretic and other principles from the posterior lobe, one should not at once conclude that they act merely by interrupting a reflex mechanism. Martin *et al.* (76) also noted the excretion of an antidiuretic substance by rats and cats during dehydration, and found greatly increased quantities in the urine of cats whose serum electrolyte pattern had become disturbed by withdrawal of cortin after adrenalectomy, or by washing out of the peritoneal cavity with isotonic glucose; it is considered that dehydration is a minor, and electrolyte imbalance a major stimulus to the posterior lobe. Obviously this suggestion, that adrenalectomy causes a compensatory increase in posterior pituitary activity, is the reverse of the conclusion drawn from the studies on chloride excretion discussed above (66). The most interesting aspect of all these studies, however, is the support they give to the view that the posterior pituitary antidiuretic hormone has a real part to play in the physiological economy of the body and is not merely a pharmacological curiosity. We may mention here the observation that (77) dehydration causes definite cytological changes in the rat's posterior lobe; that adrenalectomy does not have such an effect (44) is perhaps less significant, since we do not know what tissue it is whose water content affects the posterior lobe, and since the effect of adrenalectomy on water metabolism is so complex. Other recent experiments indicating the physiologi-

cal importance of the antidiuretic hormone may be cited; thus the interruption of water diuresis by alarming or painful stimuli follows a time course similar to the interruption by pituitrin injection (in the dog) (78), and cannot be obtained (in the rabbit) after section of the pituitary stalk (79); similar interruption of diuresis produced in the dog by acetylcholine is also dependent on the presence of the posterior lobe (80). Dehydration, produced by administering large amounts of salt, also reduces the quantity of antidiuretic substance in the rat's posterior pituitary by one half (81), while water administration increases it (82). This evidence is not unequivocal: in a long and careful investigation, Walker (83) found that while an antidiuretic substance did appear in the urine of rats on dehydration, yet this substance seemed to be more stable in urine at pH 7.2 than pituitrin is; while in the case of rabbits, cats and dogs an antidiuretic substance was separated (by adsorption on collodion) from both urine and cerebrospinal fluid, yet the amounts recovered did not depend on the degree of hydration of the animal nor even on the presence of the posterior pituitary; Walker also confirmed in cats and rats the finding of other workers with dogs, that water diuresis follows its normal time course after complete hypophysectomy. Even if one is not disposed to deny the pituitary origin of the urinary antidiuretic substance, one may have to admit that its amount has been overestimated; since pituitrin added to blood or urine may be recovered with apparently more than one hundred per cent efficiency (84) because of uptake of unidentified impurities which augment its action, probably by delaying its absorption from the site of injection. Teel & Reid (85) found an antidiuretic substance in the urine of patients with eclampsia: its presence appeared to be correlated with edema and increase of weight, rather than rising blood pressure and albuminuria; they noted certain resemblances to pitressin, and they noted also that while the substance was not normally present in the urine of healthy women in the last trimester of pregnancy, it could be caused to appear by dehydration at such times.

Complete disconnection of the pars nervosa from the hypothalamus leads, in the monkey as in other species, to permanent polyuria (86) and retrograde degeneration of the supraoptic nuclei (87).

After vagotomy and section of the cervical cord, stimulation of the hypothalamus still causes uterine contractions in rabbits (88) and a delayed prolonged rise in blood pressure in dogs (89) and cats (90): these phenomena are ascribed to release of posterior pituitary hormones. The Chinese group have continued their studies of the release of posterior lobe hormones by stimulation of the central end of the vagus, and find that during the pressor response the jugular venous blood contains an oxytocic substance, which is not obtainable in hypophysectomized animals (91) and an antidiuretic substance (92). The pressor effect gradually declines with repeated vagus stimulation and recovers with rest; these changes are correlated with the exhaustion and reappearance of secretory granules in the pituicytes (93); it has been obtained in various species, including birds and amphibia (94). It should be noted that all these experiments are conducted without the use of physostigmin, so that transmission of acetylcholine to a distance is excluded.

Shen (95) found that certain drugs, including certain barbiturates, benzodioxanes, nicotine and yohimbine, caused maximal expansion of melanophores in the normal frog (*Rana temporaria*) but were without action in hypophysectomized frogs; he concluded (96) that these substances stimulated the pars intermedia to produce its melanophore-expanding hormone; later (97) he found that the action of these drugs in normal frogs was not inhibited by destruction of the infundibulum, and concluded that they acted directly upon the pituitary without nervous mediation; cocaine and its allies were active when directly applied to the pituitary. Other drugs, such as chloroform, strychnine, physostigmin and amylnitrite, were found to be active in hypophysectomized frogs. But Teague, Noojin & Geiling, who studied the reactions to a great number of drugs in *R. pipiens*, obtained negative results even in normal frogs with many drugs previously reported to be active in one species or another: these included nicotine and the benzodioxane F 933; their most important and significant result, however, is that hypophysectomized frogs show no melanophore expansion with any drug except posterior pituitary extract for which they accordingly serve as highly specific test objects (98). There is evidence that the melanophore hormone occurs in two forms of different complexity (99).

Thyroid

Thyroglobulin and other thyroid preparations frequently exhibit a biological activity greater than their apparent thyroxine content can account for, even if one assumes that in the *d*, *l*-thyroxine commonly used as a standard one isomer is completely inactive. Since fifty milligrams of free thyroxine, administered orally, may be no more effective in raising the metabolic rate in myxedema than 0.33 mg. intravenously (100), while crude thyroid preparations are necessarily given by mouth, direct comparisons are difficult. It is certain, however, that some explanatory hypothesis is required: either thyroxine acquires enhanced potency in its "natural setting" in the polypeptide chain, or diiodotyrosine, inactive in the free state, is calorigenically active in some specific combination. In 1931, Blum claimed that he had obtained protein fractions from the gland which were far more active, per unit weight of iodine, than ordinary preparations; but this has not been confirmed (101). Wokes (102) exposed tadpoles to suspensions of various desiccated thyroid powders, and used the decrease in body length as a criterion of potency. He found the ratio of potency to total organic iodine less variable than the ratio of potency to thyroxine in his powders, and as usual the potency was anomalously high. Meyer & Wertz (103) administered thyroxine and various other preparations to normal and thyroidectomized male rats, finding the latter twenty-five times more sensitive, and less variable in response. They administered their preparations by stomach tube, in alkaline solution when necessary, daily for three days, and measured the resting oxygen consumption on the fifth day, obtaining a logarithmic relation of response to dose. The dose required to produce a 25 to 30 per cent increase in the oxygen consumption of thyroidectomized rats was only about one-fifth of that required to restore their metabolism to normal levels (45 to 50 per cent increase), and was about 7.5 μg. of *d*, *l*-thyroxine per 100 gm. daily, whereas a purified thyroglobulin was equally effective in doses containing only 2.3 μg. of *l*-thyroxine. The potency of various preparations and split products paralleled neither the thyroxine content nor the total iodine content. Bradycardia is characteristic of thyroidectomized rats, and it has been found (104) that daily injections of 40 μg. of *d*,*l*-thyroxine restore the heart rate to normal. The weight of the rats was not stated.

Meyer (105), however, found that doses of thyroxine or thyroglobulin that restored oxygen consumption to normal had only a slight effect on the bradycardia, and in a later note (106) concludes that thyroxine may he purified to the point at which it has almost no effect on heart rate, while accelerating fractions may be obtained that have little calorigenic action. The failure of the heart in experimental hyperthyroidism is not due to exhaustion of glycogen (107). It is generally agreed that thyroxine added to tissues *in vitro* does not increase their oxygen consumption, but since thyroglobulin itself is active in such experiments (108) one cannot conclude that there is nervous mediation of the calorigenic stimulus. It seems perfectly possible that free thyroxine has no calorigenic effect at all, and that its activity in intact or thyroidectomized animals depends upon its incorporation into a polypeptide or other complex; such a theory would go far to explain the paradoxes discussed above, but must unfortunately be hard to verify or to disprove. An important and surprising discovery, which may also be relevant to these problems, was made by Ludwig & von Mutzenbecher (109) and immediately confirmed (110). They found that iodination of casein under special conditions yielded a product which not merely possessed calorigenic activity (111) but actually permitted the isolation of thyroxine, in quantities of one milligram per gram, after hydrolysis. Whether this indicates that thyronine (desiodothyroxine) is a hitherto undetected constituent of casein, and can be completely iodinated under these conditions; or whether the iodine has an oxidative action on the side-chain as well as its substitutive action in the ring of tyrosine, and thus permits the oxidative coupling of two molecules of diiodotyrosine, is uncertain; neither view is very attractive at first sight. While the total iodine content of the treated casein is, of course, very high (eight per cent), the relation between the calorigenic effect in rats and the amount of thyroxine isolated (110) is approximately the same as the ratio of the activity of thyroglobulin to its thyroxine content (103).

McClendon (112) applies the term "hormone iodine" to the fraction (about two-thirds) of the total blood iodine which is not extractable with methyl alcohol and acetone, and affirms (113) a statistical relation between this and the basal metabolic rate, so that an increase of 0.2 μg. hormone iodine per 100 ml. corresponds to an increase in basal metabolic rate of one kilocal per sq. m. per

hour. The extractable iodine or "iodide reserve" tends to vary inversely so that the total is constant. Blood iodine has also been divided into three fractions: acetone-soluble, water-soluble, and insoluble (114). But methods for determining blood iodine are still in a somewhat unstable state, and the trend to lower values, around 3 μg. per 100 ml., continues (114, 115, 116); there are possibly regional variations, but it seems evident that two laboratories, in each of which consistent values are obtained, may obtain very different average results.

The relation between the thyroid gland and the vitamins has received much study. Large amounts of vitamin A inhibit the action of thyroxine (but not of dinitrophenol) on the basal metabolic rate (117), and tend to produce thyroid hypoplasia with an increase in the amount of thyrotrophic hormone in the anterior pituitary (118, 119). In B_1-deficiency in the rat, the thyroid becomes inactive and the thyrotrophic potency of the anterior lobe falls (120); this is not due merely to decrease in food intake (121), and is accompanied by a fall in gonadotrophic potency (122); we may refer here to the use of the rat in dietary anestrus for the assay of gonadotrophic hormones (123). Thiamine (aneurin) decreases the metabolic, but not the histological response to thyrotrophic hormone in the guinea pig (124), and tends to prevent loss of weight in experimental hyperthyroidism (125). The scorbutic guinea pig's thyroid is more than usually sensitive to thyrotrophic hormone (126); on the other hand, administration of thyroid or thyrotrophic preparations decreases the concentration of ascorbic acid in the liver and adrenals of the guinea pig, and in human subjects there is an inverse relation between the metabolic rate and the percentage recovery from the urine of a large injected dose of ascorbic acid (127). The relation between the thyroid and vitamin E will be referred to below.

Parathyroids

Though the clinical literature is increasing rapidly, the parathyroids have not received much physiological study in the period under review. Methods of biological assay, still far from satisfactory, have been reviewed. Bliss & Rose (128) studied Miller's data statistically; the rise in serum calcium in the dog is proportional to the logarithm of the dose, but individual variation can only be controlled by testing each animal with an arbitrary "standard"

preparation as well as with the unknown to be assayed; this treatment makes it unnecessary to determine the pre-injection level of serum calcium. The increase in urinary calcium in rats injected with parathyroid hormone is also proportional to the logarithm of the dose (129), and, as Dyer and Pugsley suggested independently some time ago, provides an inexpensive alternative method of assay. A novel but very indirect assay method is proposed by Wallbach (130), who finds that in rabbits pre-treated with parathyroid extract an injection of *E. coli* evokes a lymphocytosis proportional to the dose of the hormone. It is clear that present assay methods leave much to be desired; an international standard preparation would be most helpful, if sufficiently stable, but possibly demands some further advance in methods of purification.

There appears to be a direct action of the parathyroid hormone upon the excretion of phosphate by the kidney. When the kidney of a parathyroidectomized dog is transplanted, forty-eight hours after operation when phosphate excretion is falling rapidly, it excretes much less phosphate than the transplanted kidney of a normal dog perfused with the same blood at the same time (131). We entirely agree, however, with those who conclude that this action of the hormone is wholly distinct from and independent of its action in mobilizing calcium from the skeleton (132, 133).

Gonadotrophic Hormones

We wish to draw attention to the recent report on standardization of gonadotrophic hormones (134, 135), which set up an international standard of the chorionic (pregnancy urine) hormone, and prepared the way for similar steps to be taken with the mare-serum principle, and the thyrotrophic hormone; other pituitary hormones, it was felt, could not be handled in this way with profit at the present time. It is in agreement with this report that we have adopted the spelling "trophic" rather than "tropic" throughout this review. Since we have dealt elsewhere (136) with the whole topic of "anti-hormones," we have omitted it altogether from these pages. We may take this opportunity of welcoming an admirable review (137) of the whole field of pituitary physiology.

The production of intersexes by administration of gonadal hormones during embryonic life was discussed in last year's review. Desoxycorticosterone was found to have no such effect (138), but it enhanced the activity of testosterone; the androgenic

properties of progesterone (139, 140) have not been tested directly in this way, but may conceivably explain the masculinization observed in newborn female rats treated with gonadotrophic preparations (141 to 145). Attention may also be drawn to evidence that the pituitary is not essential for the early development of the sex organs of the unhatched chick (146, 147).

Grumbrecht & Loeser have elaborated a novel and complex theory of the origin of ovarian cyclicity. They believe that the hypophysis produces gonadotrophic hormones at a constant rate, but that the responsiveness of the ovary varies; increased responsiveness is due to the presence of a temporary excess of thyroid hormone; the temporary increase in thyroid activity is due in turn to the excess of estrogenic hormone liberated at ovulation; this however acts upon the thyroid, not directly, nor merely by way of pituitary thyrotrophic hormone, but rather by way of the uterus; in the uterus, estrogens either cause the liberation of, or are converted into, a substance having thyrotrophic properties, or, more probably, stimulating the pituitary to produce thyrotrophic hormone. The evidence supporting this construction is of many kinds. They declare in the first place that there are no variations in the gonadotrophic hormone content of the rat pituitary during the estrus cycle; secondly, they show that the effect of anterior lobe preparations (but not of pregnancy-urine preparations) on the ovaries of immature rats is much enhanced by pretreatment with thyroxine (5μg. daily, subcutaneously) or thyroid colloid, and indeed thyroxine renders the infantile rat precociously responsive to its own gonadotrophic hormones; the effect of thyroxine is upon the ovary, not on the pituitary, whose gonadotrophic hormone content is unaffected (148). They point out also that in the rat and mouse, the formation of the ovarian capsule forces follicular fluid at ovulation to pass down into the uterus, where the estrogens present will act with great intensity—it was, indeed, possible to demonstrate an action of estrogens upon isolated uterine tissue *in vitro* (149). The importance of this direct contact is brought out in several ways. They have shown (150) that if it is prevented (by ligation of the tubes or decapsulation of the ovaries), the thyroid passes (as after ovariectomy) into a quiescent state with flattened epithelium and large colloid filled follicles; this quiescence can be stirred up by introduction of estrogens into the uterus, but not by subcutaneous injections.

Similarly, the quiescent thyroid in avitaminosis-E can be activated by estrogens only when they are given directly into the uterus, while vitamin E itself is effective by any route but has no action on the thyroid of the castrate rat (151). In normal rats, intrauterine application of estradiol benzoate increased the thyrotrophic hormone content of the pituitary (152), and though there was little obvious change in the thyroid, the ovaries became filled with corpora lutea, which is regarded as a result of sensitization by an increase of thyroid hormone. Next, the effects of hysterectomy are interpreted in terms of the theory: these effects (148) differ from those of ovariectomy in that there is no prolongation of the period of rapid growth, and no increase in the gonadotrophic activity of the pituitary; but they are similar in that in both cases there is an early quiescence of the thyroid as judged both from histological evidence and from a fall in resting oxygen consumption of the animals, and a delayed but progressive increase in the size of the anterior lobe and in its total thyrotrophic activity. Hysterectomy also causes a transient decline in ovarian activity, with anestrus, interpreted as a sign of ovarian refractoriness during hypothyroidism. Later, as the thyrotrophic content of the pituitary increases, the metabolic rate returns to normal and the thyroid epithelium becomes higher and more active; ovarian function is resumed and many corpora lutea are formed, while estrus reappears though it may be very irregular. All this is regarded as the body's endeavour to compensate for the loss of the thyroid stimulation supposed to emanate from the uterus; but it is not apparent why the accumulation of thyrotrophic hormone in the pituitary after ovariectomy does not, as after hysterectomy, reawaken the quiescent thyroid; one feels also that the theory predicts a greater disturbance of estrous rhythm after hysterectomy than is, in fact, observed. In the last group of experiments (148), it is shown that while implantation of adult uterine tissue under the dorsal skin of immature rats has no ovary stimulating effect, it does sensitize the ovaries to subthreshold doses of anterior pituitary extract; this effect is ascribed to estrogen present in the uterine tissue, since it is enhanced if extra estradiol is injected into the implanted uterine tissue; it is claimed further that the effect is specific for uterus, that stilbestrol cannot replace natural estrogens, and that contact between hormone and uterine tissue

is essential. Thence it is concluded that the estrogen is either transformed into, or causes the production of a thyrotrophic substance unidentified, which promotes relative hyperthyroidism which in turn sensitizes the ovaries to gonadotrophic stimulus. New and challenging data abound in this work, though one may not feel that the authors' interpretation is the only one possible; and much emphasis is laid on assays of the hormone content of the pituitary, which are not easy to make accurately and are still harder to interpret unequivocally. It may be noted here that hysterectomy slightly raises the vaginal threshold to estrogenic stimulation (153).

Several papers published in the period under review have a bearing on this theory; if the chorionic gonadotrophic hormone displays a delayed thyrotrophic effect in guinea pigs (154), that might be interpreted as a secondary response to increased estrogen liberation. On the other hand, the observations that the responsiveness of the rat ovary to gonadotrophic stimuli is increased by thyroidectomy (155), and that of the testis (156) and ovary (157) decreased by thyroxine pre-treatment, seem to be directly opposed to the views of Grumbrecht & Loeser. In fowls (especially males) however, thyroidectomy decreased either the production of gonadotrophic hormones or the responsiveness of the gonads (158). The gonadotrophic activity of the anterior pituitary in the female rat was clearly shown to be greater before puberty and in age than during active reproductive life (159), but the effect of estrus was not studied.

Some workers (160, 161) have been unable to separate distinct follicle stimulating and luteinizing fractions from pituitary extracts, and feel that the response to a single active principle may be so modified by the site of injection, division of the dose, presence of inert proteins in the extract, the initial state of the ovaries of the test animal and other factors, that the existence of two separate gonadotrophic hormones in the anterior lobe is not satisfactorily established. Moreover, the test animal's own pituitary may participate in many of the biological reactions which have been studied, and confuse the picture. These criticisms and objectives have, to a large extent, been met in more recent work; but it is important to note the exact nature of the newer tests. Both Fevold (162) and Jensen, Evans, Simpson & Tolksdorf (163) have

described improved methods for separating the luteinizing hormone (LH) from the follicle stimulating (FSH), which depend on the relative insolubility of the former in ammonium sulphate solutions at pH 4.2 or 5. Studies on the properties of the fractions obtained have also been reported from both laboratories (164, 165). The luteinizing hormone, though inactive by itself in immature or hypophysectomized female rats, "produces corpora lutea if injected with follicle stimulating hormone or if given to animals whose ovaries have undergone considerable follicular development" (162), but this is not the basis of the tests now chiefly employed. Fevold assays follicle stimulating hormone in terms of the increase in ovarian weight in intact immature rats; but this test is applicable only to extracts from which luteinizing hormone has been almost completely removed (so that the ovaries show purely follicular development), because luteinizing hormone augments the action of follicle stimulating hormone on ovarian weight, and when sufficiently purified may indeed be assayed by its power to increase the activity of purified follicle stimulating hormone. Such tests are suspect, because the apparent activity of the latter may be enhanced by addition of various materials which delay absorption from the site of injection (166), such as zinc or epinephrine. The effect of the luteinizing hormone, however, is specific, in that it is evident when the two principles are injected separately at different sites. Fevold (162) reports that 0.1 mg. luteinizing hormone increases the effect of 0.15 mg. follicle stimulating hormone, which by itself yields ovaries weighing 20 mg., so that the ovarian weights obtained are 73 mg. when the two solutions are mixed, or 68 mg., when they are given separately; while 0.2 mg. of the luteinizing hormone by itself is without action. Evans *et al.* (165) obtained similar evidence of synergistic action despite separate injection, in hypophysectomized female rats. Yet the fact that luteinizing principle has a true synergistic effect, not dependent on delaying absorption, does not exclude the possibility that non-specific augmentations may occur when two extracts are combined, and be erroneously taken as a measure of luteinizing hormone activity.

Attempts have therefore been made to find more specific reactions of the luteinizing hormone, not dependent on co-operation with extracts of the follicle stimulating hormone assumed to be

pure. Fevold therefore assays the luteinizing hormone by its power to stimulate the interstitial tissue of the testes of immature male rats, which in turn is measured by the weight of the seminal vesicles. His follicle stimulating preparations do not give this reaction in moderate doses, though when added to luteinizing extracts they increase their potency both in normal and hypophysectomized rats (164). It will be seen that this is really a test for the interstitial cell stimulating hormone (ICSH) of Evans, but apparently Evans himself now accepts the identity of his ICSH (though he continues to use the term) with luteinizing hormone as ordinarily understood and as discussed in the previous paragraph; there is, of course, no rigid proof of identity as yet, but no one will wish to "multiply entities beyond necessity." Evans & Jensen assay their extracts upon prepubertal rats hypophysectomized a week before testing; follicle stimulating hormone causes resumption of development of healthy follicles with small antra, while ICSH "causes repair of the deficient interstitial tissue of the ovary" with abolition of the wheel-like pattern of the chromatin in thecal and related cells (163), though ovarian weights are also reported. Fevold uses ovarian weights of normal immature rats as a test for follicle stimulating hormone.

The results of these later studies undoubtedly support very strongly the theory that there are two distinct and separable gonadotrophic principles in the anterior pituitary. Both groups of workers have obtained far-reaching separation of follicle stimulating and luteinizing (or ICSH) activity, as defined by their tests; on the other hand, a very large part of the original gonadotrophic activity of the first extractions is lost during the purification; the final preparations, when combined together, are much less active per gram of original tissue (though much more active per milligram of total solid matter in the solution) than crude extracts are, which undeniably weakens the argument somewhat. Fevold (164) finds that follicle stimulating hormone, but not luteinizing hormone, is reversibly inactivated by precipitation with picrolonic, picric or flavianic acids; picrolonates of unfractionated extracts therefore have little action on ovarian weight, while their effect on seminal vesicle weight is reduced only by loss of the very considerable augmenting effect of follicle stimulating hormone on luteinizing hormone activity in this test. He

also finds that follicle stimulating hormone is ineffective when injected intraperitoneally, while luteinizing hormone is as active by this route as it is subcutaneously. Evans (165), however, finds that though follicle stimulating hormone is less potent intraperitoneally than subcutaneously in intact rats it is not by any means inactive, and in hypophysectomized rats there is little difference between the two methods of application, while interstitial cell stimulating hormone is decidedly more active intraperitoneally.

The luteinizing hormone of Fevold & Fiske (167) and interstitial cell stimulating hormone of Evans *et al.* (165) both have the property that when injected intraperitoneally they diminish the effect of follicle stimulating hormone or of mare-serum extract (165) injected subcutaneously; this antagonism is seen also in hypophysectomized rats. It is agreed that there is at present no reason to regard the "antagonist" as a separate substance, although elsewhere it has been claimed that the antagonist survives boiling at low pH which destroys both gonadotrophic hormones (168). The mechanism of the antagonism is obscure: Fevold & Fiske conclude that it is not a matter of making the ovaries themselves directly refractory to follicle stimulating hormone (167), and the significance of the route of injection is unexplained.

The chorionic gonadotrophic hormone (prolan) has been compared by Evans *et al.* (165) with the interstitial cell stimulating hormone fraction, which it closely resembles in its power to repair interstitial tissue in the ovary of the hypophysectomized rat, and in augmenting the effect of follicle stimulating hormone on the ovaries of hypophysectomized rats when both are injected separately subcutaneously; but prolan has far more action on the ovaries of normal immature rats than interstitial cell stimulating hormone, and when injected intraperitoneally it does not show antagonism to the follicle stimulating action of pregnant mare serum given subcutaneously. For these and other, especially chemical, reasons, the pituitary interstitial cell stimulating or luteinizing hormone is regarded as different from the chorionic hormone prolan. The gonadotrophic hormone in chorioepithelioma urine is identical with pregnancy-prolan (169) but of course unlike that in menopausal urine, from which, it is claimed (170), synergistic and antogonistic fractions may be separated.

Chemical and enzymatic methods of differentiating gonado-

trophic hormones have been explored further. Unfractionated gonadotrophic extracts of the anterior lobe produced a more purely follicle stimulating effect and little luteinization, after partial digestion with trypsin (171, 172, 173); immersion in formalin for some days similarly changes the effects of anterior-pituitary implants (174, 175). If there were no independent evidence of the existence of a specific luteinizing hormone, one could easily interpret these experiments as non-specific, and dependent, for example, on the rate of absorption of follicle stimulating hormone. Quite different results were obtained by Abramowitz & Hisaw (176), who found pregnancy-prolan more sensitive to chymotrypsin and papain than either gonadotrophic hormone from sheep pituitaries, and the luteinizing hormone most resistant to papain and ptyalin; in this case luteinizing hormone was tested by Fevold's method (seminal vesicle weight). The assumption that it is actually the same substance as the luteinizer found by others to be especially trypsin-sensitive seems to require verification. Trypsin destroyed the gonadotrophic activity of a sheep pituitary extract, but not its power to enhance the activity of chorionic prolan injected at a different site (177). The effect of alkaloidal reagents on follicle stimulating hormone has been mentioned (164). Cystein was found (178) to destroy all gonadotrophic activity in extracts of anterior lobes or of normal male urine or post-menopausal urine, but to have little action on preparations from human pregnancy urine or pregnant mare serum. Evans *et al.* (179) also found that follicle stimulating preparations were very rich in carbohydrate (principally glucosamine) when compared with interstitial cell stimulating and other purified pituitary hormones, but not when compared with some inert pituitary proteins; and chorionic prolan, as is well known, contains much carbohydrate, apparently galactose and hexosamine (180).

The effect of various gonadotrophic preparations in the immature female *Macaca mulatta* and *M. irus* has been re-investigated by de Fremery (181), who found that extracts from hog or human pituitaries, or from human menopausal urine, caused marked cystic development of follicles and appearance of all external signs of full estrus; while preparations from human placenta or pregnancy urine had no action at all, not even modifying the effect of the hog pituitary extract, although they did cause some en-

largement and descent of the testes in an immature male. Noble *et al.* (182) found that immature hypophysectomized female rats responded to human pregnancy urine and ox pituitary extracts by luteinization only, to human pituitary extracts by follicular growth only, and to pituitary extracts from horse, sheep, and hog by follicular development and luteinization; such "mixed" responses were obtained with all the extracts in immature intact rats, whose own anterior lobes must have participated in the reactions. In more detailed studies, pregnant mare serum extracts were found to maintain the gonads of adult male (183) and female (184) hypophysectomized rats better, and for a longer time, than pregnancy urine preparations; the extracts were assayed by different methods, and one cannot be certain that the doses were equivalent. Fluhmann (185) treated immature female rats for long periods with gonadotrophic preparations from (1) the anterior lobes of sheep, (2) human pregnancy urine and (3) the serum of pregnant mares. In the first case the increase in ovarian weight was great, but was followed by great atrophy despite continued injections; in the second case the weight increase was even greater, and more lasting, and the subsequent atrophy was late and never complete; in the third case there was comparatively little ovarian growth, but greater enlargement of the uterus than in the two other series.

An interesting analysis of the pathways involved in the effect of light upon the hypophysis has been published (186). While normal female ferrets came into heat in April, May or June, or even in late January or early February if exposed to artificial illumination, ferrets blinded by section of the optic nerves in November or December displayed estrus very late, if at all, despite extra illumination. On the other hand, illumination had its usual accelerating influence in a series of ferrets in which various brain operations were performed during the winter: these operations included removal of the visual cortex (with almost complete degeneration of cells in the lateral geniculate bodies), and complete isolation of the anterior corpora quadrigemina and pretectal areas from retinal connexions. Hence "the normal response of the pituitary to retinal stimulation depends on impulses passing either to the ventral nucleus of the lateral geniculate body (which . . . is considered to be a lateral extension of the subthalamus), or to the subthalamus

by way of the accessory optic tracts." It is pointed out that there are fibre paths which could carry impulses from the subthalamus to the posterior lobe of the pituitary, but there is little histological evidence of these paths continuing into the anterior lobe (187). On the other hand, physiological evidence for transmission of impulses to the anterior lobe through the infundibulum was cited in last year's review, and it has been shown recently (188) that section of the pituitary stalk in rats prevents the usual hyperplastic response of the thyroid to cold, though it does not lead to atrophy of the thyroid or other glands dependent on pituitary stimulation. An intact infundibulum is also said to be essential for estrogens to cause mammary development in the male rat (189). Meanwhile Benoit & Kehl (190) have repeated and extended the surprising observation that direct illumination of the hypophysis and hypothalamus stimulates testicular development in immature drakes.

Growth Hormone

Freud & Levie (191, 192) find that when young rats are hypophysectomized, growth in length of the tail and development of caudal vertebrae cease altogether, but will continue if the animals are at once treated with purified growth hormone preparations. The response is less variable than the simultaneous increase in total weight, and is more or less proportional to the dose, so that it can well be used for assay purposes. The reviewers have long felt that a test based on skeletal growth would be preferable to those based on body weight, which varies with hydration and many other factors. However, thymus extracts also give a positive result in this test (193). Freud points out that treatment must be commenced immediately after hypophysectomy, otherwise irreversible closure of the epiphyses occurs. This is somewhat surprising in view of the work of the Silberbergs (194, 195) who find that anterior pituitary extracts promote hypertrophy and hyperplasia of cartilage and epiphyseal closure in guinea pigs, and who ascribe the similar effects of castration to the resulting increase in anterior lobe activity. However, it is probable that the extract used by them was complex and not even approximately a "pure" growth hormone. Freud's work is a notable support to the view that there is a pituitary hormone specifically concerned with growth, and skeletal growth in particular. Evans *et al.* (196) have

reaffirmed their stand on this question: although thyroid preparations promote growth in thyroidectomized animals and in silver dwarf mice, they differ from anterior pituitary extracts in having no such action in thyroidectomized hypophysectomized rats; a supply of thyroid hormone, endogenous or exogenous, is essential for maximal growth in all cases, but without it positive responses to anterior pituitary growth hormone can still be obtained. Moreover, growth hormone preparations can be almost completely freed from thyrotrophic hormone and prolactin by exposure to the reducing action of cystein (197).

Hormones and Carbohydrate Metabolism

In the confused and complicated question of the relation of the anterior pituitary to metabolic processes in general and carbohydrate metabolism in particular, progress is slow and tentative: the great obstacles to rapid clarification being the difficulty of separating the various pituitary hormones from one another, and the almost astounding individual variations in animals in experiments of this type. Three topics with which the recent literature has been concerned may be designated as follows: (*a*) the tendency of hypophysectomized animals to pass into hypoglycemia and to exhaust their stores of carbohydrate in fasting; (*b*) the extreme sensitivity of the hypophysectomized animal to insulin, and the resistance to insulin conferred by pituitary extracts; (*c*) the power of certain pituitary extracts some or all of which have been called "diabetogenic," to produce hyperglycemia and glycosuria, sometimes ketonemia and ketonuria in various species under various circumstances and, undoubtedly, in various ways.

Under the first heading, we may note that there is a decided resemblance between the hypophysectomized animal and the adrenalectomized animal (at least when the disturbance of water and salt metabolism produced by adrenalectomy is partly controlled); in both there is a tendency for blood sugar to fall to low levels in fasting, and for carbohydrate stores to be rapidly exhausted. This similarity naturally induced many students to consider that the fasting hypoglycemia of the hypophysectomized animal was a consequence of atrophy of the adrenal cortex, and to discount the existing evidence that pituitary extracts which con-

tained the "glycostatic" principle and prevented this rapid depletion of carbohydrate might be devoid of adrenotrophic effect as usually assayed by adrenal weight or histological changes, and might be active even in the absence of the adrenals. Those who inclined to this point of view were doubtless confirmed in their opinion by demonstrations that cortical extracts (198, 199, 200) or synthetic desoxycorticosterone (201) could maintain blood sugar and liver glycogen during fasting in hypophysectomized, almost as well as in adrenalectomized rats. It is true that cortin does not easily elevate muscle glycogen levels after hypophysectomy, but then it is not efficient in this respect even after adrenalectomy (200), so that the two conditions can not be qualitatively differentiated by this test.

When normal rats are fed glucose after a twenty-four hour fast, about one-half of the absorbed glucose is oxidized, one-third is stored as liver and muscle glycogen in approximately equal shares, and one-sixth is "not recovered." Cortin decreases the proportion oxidized, inhibiting the usual increase in respiratory quotient, and increases the proportion stored (200). Adrenalectomized rats, as compared with normals, store less and oxidize more; cortin treatment increases the storage, especially in the liver, and decreases the proportion oxidized even below the normal 49 per cent; anterior pituitary extract known to display "glycostatic" activity somewhat favours storage as glycogen in the muscles although not in the liver but does not noticeably check the excessive oxidation. However, such extracts, given along with cortin, greatly diminish the proportion of the fed sugar which is oxidized, and cause as much as one-third to be deposited as muscle glycogen (202). This demonstration that pituitary extracts have an influence on carbohydrate metabolism dependent on the simultaneous presence of cortical hormone, but not acting through the adrenal cortex, is obviously very important. It suggests that hypophysectomy depresses adrenal activity but conversely adrenalectomy renders pituitary hormones impotent. One might speculatively consider that cortical hormone is immediately necessary for maintenance of liver glycogen, but helpful only as an adjuvant to a true pituitary glycostatic hormone for the maintenance of muscle glycogen; and quote in support the observation (203) that muscle glycogen instability is evident after hypophysectomy more rapidly

than after adrenalectomy, and that large amounts of pituitary extract maintain muscle glycogen but not liver glycogen in hypophysectomized-adrenalectomized rats; if they maintain liver glycogen in rats that have merely been hypophysectomized, that may be due to some contaminating adrenotrophic hormone, though there are real objections to this interpretation.

The decline of blood sugar and of carbohydrate stores in general after hypophysectomy has been regarded on the one hand as an indication of increased carbohydrate oxidation, and on the other hand as a sign of diminished gluconeogenesis. Analyses of entire carcasses and measurements of the respiratory quotient of intact animals obviously cannot readily distinguish between these theories; perhaps the best evidence for the first named view is just that when glucose is fed to fasted hypophysectomized rats, the proportion immediately oxidized is greater than in normal or even adrenalectomized animals, which perhaps indicates a general inclination of hypophysectomized animals to oxidize carbohydrate in preference to fat. On the other hand one can scarcely doubt that gluconeogenesis is diminished. Some writers apparently regard gluconeogenesis as a detour through which products of protein catabolism can be diverted, or from which they can be excluded, under some endocrine control; but surely it is more orthodox to suppose that a fairly constant proportion of the amino acids liberated in protein breakdown are inevitably transformed into substances which are intermediaries in carbohydrate metabolism, and therefore that nitrogen excretion is a measure of gluconeogenesis—unless one is willing to admit that a large and variable proportion of the new formed carbohydrate is derived from fat. On this basis the decreased nitrogen excretion of the hypophysectomized animal is sufficient sign that gluconeogenesis is decreased, and moreover angiostomy experiments do indicate that the discharge of glucose by the liver is reduced by one-half after hypophysectomy (204). One would also expect to find glycine and other sugar forming amino acids converted into carbohydrate as completely, but not necessarily as rapidly, as ever despite loss of hypophyseal hormones, and indeed no inhibition is observed (204). Decreased gluconeogenesis in fasting, then, would be the necessary consequence of a decrease in the rate of breakdown of tissue proteins and in the supply of amino acids for deamination, and one

would expect to observe this in any state of hypothyroidism, such as that produced by hypophysectomy. Thus Soskin, Levine & Heller (205) find that thyroxine will prevent the fall of blood sugar of the hypophysectomized dog in inanition, just as it increases the nitrogen excretion. However, the hypothyroidism of the hereditary dwarf mouse does not cause it to show marked fasting hypoglycemia (206). Adrenal cortical extract also increases the nitrogen excretion and the carbohydrate content of fasting normal, adrenalectomized or hypophysectomized rats (200) in equivalent amounts, and the complicity of the adrenals in the hypoglycemia of hypophysectomy is too firmly established to be lightly disregarded. The interrelations between the thyroid and the adrenal cortex have not yet been clearly worked out. Thyroidectomy would presumably reduce both the supply of carbohydrate from tissue protein (207), and the removal of carbohydrate by oxidation. Selye (208) finds that the blood sugar of thyroidectomized rats falls faster than normal in the first twenty-four hours of fasting, but not thereafter; is it possible that thyroid hormone affects protein breakdown more rapidly than it does carbohydrate oxidation, and that in Soskin's experiments the acceleration of oxidation by thyroxine had not caught up with the acceleration of protein breakdown and gluconeogenesis? Using the rate of increase of non-protein nitrogen in the blood after nephrectomy as an index of the rate of protein catabolism, Mirsky (209) finds it to be doubled by pancreatectomy, and then still further increased by anterior pituitary extracts which have no such influence when the pancreas is present. In normal fasted rats, on the other hand, crude anterior lobe extracts may decrease protein catabolism to the point where hypoglycemia and ketosis appear (210), and some such restraint on catabolism is obviously required of a "growth hormone." Be it noted in conclusion that granting a decrease in gluconeogenesis after hypophysectomy does not entail denying an increased tendency to utilize carbohydrate peripherally; but Soskin, Levine & Lehmann (211) have measured sugar utilization in eviscerated dogs by the amount of glucose infused to maintain a predetermined blood sugar level, plus decrease in muscle glycogen, minus increase in lactic acid content of the carcass, and find it to be unaffected by anterior pituitary extract (phyone) but subnormal, at all blood sugar levels, after hypophysectomy. One may

question some of the calculations, for instance, the factor used in estimating total lactic acid content from the concentration of lactate in blood, and feel that the conditions are very unphysiological, but the results of these studies are indubitably consistent. Since the animals were acutely eviscerated one would hardly suppose that they lacked insulin: yet these experiments contrast with an earlier demonstration (212) that hypophysectomized rabbits require large quantities of glucose to maintain their blood sugar, even at relatively low levels where glycogen formation should not take place. It has since been shown (213) that this large glucose requirement is much reduced by injection of quite small amounts of mixed amino acids; this is a disturbing observation which casts some doubt on demonstrations of the "sugar-forming" powers of amino acids, and suggests new theories of the action of hormones in carbohydrate metabolism; it is to be hoped that its significance and limitations will soon be explored. There is, of course, much evidence that a carbohydrate plethora decreases protein catabolism and gluconeogenesis (207).

It is well known that hypophysectomized animals are extremely sensitive to insulin, and that pituitary extracts can make normal animals insulin resistant. Himsworth & Scott (214) found that such extracts did not retard the spontaneous fall in blood sugar in hepatectomized rabbits, but prevented acceleration of that fall by insulin; likewise Russell (215) found that they did not inhibit fasting hypoglycemia in hypophysectomized rats, but did prevent insulin hypoglycemia. This suggests that these "glycotrophic" preparations do not especially retard carbohydrate oxidation, but either inactivate insulin directly, one possible mechanism suggested having been that insulin is inactivated by the liver glutathione, which is reduced in amount by hypophysectomy (216); or else they inhibit the formation of muscle glycogen, which insulin promotes, in which case there is an apparent contrast with the "glycostatic" effect shown by the same pituitary extract.

Russell also made the important observation that insulin decreased oxygen consumption in the hypophysectomized rat, whether fasted or glucose fed, although in the latter case the effect on blood sugar was slight. She suggested that in the normal animal insulin increases carbohydrate oxidation and equicalorically decreases fat oxidation, while in the hypophysectomized animal sup-

plied with glucose carbohydrate oxidation is already maximal and insulin acts merely to inhibit fat oxidation. On this basis the "glycotrophic" or "anti-insulin" factor should act as a specific stimulant of fat oxidation, since the extracts tested restored the oxygen consumption of insulin-treated fasted or fed hypophysectomized rats, even beyond normal levels. It is therefore relevant here to note the demonstration by O'Donovan & Collip (217, 218) of a pituitary factor which causes a rapid increase in metabolic rate, independent of the thyroid gland and of thyrotrophic activity, of rabbits and guinea pigs, associated with a fall in respiratory quotient which suggested depression of carbohydrate oxidation as well as increase of the combustion of fat. The principle was found most richly in pars intermedia extracts and in pituitary colloid, and in its properties as well as its distribution closely resembled the melanophore-expanding hormone. Both effects are manifested by extracts which have largely been freed from the "accepted" anterior pituitary hormones by exposure to temperatures of 100°C. Such preparations also display various metabolic effects: they evoke ketonemia in normal or adrenalectomized rats, they decrease total body fat but increase liver fat in fasted mice, they increase glycosuria and ketonuria in the hypophysectomized-depancreatized dog, they maintain liver and muscle glycogen during fasting in guinea pigs and normal and hypophysectomized rats and are therefore glycostatic; and last but not least relevant, they render rabbits resistant to insulin and are therefore glycotrophic (219, 220). The stability of the anti-insulin factor to heat has been noted elsewhere (221). It seems, therefore, that such extracts possess the properties required of a pituitary hormone in Russell's experiments.

When crude pituitary extracts, made from fresh glands and protected from any elevation of temperature, are injected into dogs, they produce glycosuria and other signs of diabetes, which gradually vanish in spite of continued treatment at a constant dose level; but if the dose is progressively increased the diabetic state continues and becomes permanent and irreversible (222); this is due to the production of degenerative changes in the islets of Langerhans, which go so far that the pancreas is almost insulin free, and the diabetic state is not further aggravated by its removal (223). The temporary diabetes may be observed even in

rats, but it does not become permanent (224) and the insulin content of the pancreas is actually increased (225). It is especially to be noted that this type of "diabetogenic" action is not obtainable with purified or even mildly heat-treated anterior pituitary fractions (226, 227).

On the other hand, another type of response frequently called "diabetogenic" is much more easily elicited, and is evidently entirely different, not merely due to survival of traces of the labile factor, detectable only in very sensitive preparations: this is the increased glycosuria and ketosis produced when depancreatized-hypophysectomized dogs or cats are treated with pituitary extracts. Since such extracts are usually ineffective in depancreatized-adrenalectomized animals, which otherwise closely resemble the Houssay preparation (228), Long and others have felt that their activity depends on stimulation of the adrenal cortex, presumably by the adrenotrophic hormone as ordinarily defined; and this view is supported by the finding that cortical hormone similarly aggravates the diabetes of the rat with subtotal removal of the pancreas (229). This observation, however, was coupled with the warning that still further aggravation was produced by treatment with anterior pituitary extract in addition to cortin. Houssay & Biasotti (230, 231) also reported the activity of anterior lobe extracts in a subtotally-depancreatized-adrenalectomized dog; moreover, it does not appear that all the extracts which have been found active contain the adrenotrophic hormone. It seems, therefore, that we must distinguish three methods by which anterior pituitary extracts may produce hyperglycemia and glycosuria: by depression of the islet tissue, which may become irreversible; by stimulating the adrenal cortex; and by some action presumably direct, such as inhibition of carbohydrate oxidation. The relative importance of these in normal physiology is impossible to evaluate; nor is it easy to correlate them with the "ketogenic" phenomenon, the evocation of ketonuria and ketonemia in fasting or fat fed rats; ketosis can be produced in so many ways that this phenomenon is very probably complex. Adrenalectomy, as is well known, may almost abolish the ketonuric response to anterior pituitary extracts; this is partly due to the difficulty the adrenalectomized animal seems to have in excreting acetone bodies, which is also shown by the hypophysectomized rat (232); but the keto-

nemic response is also reduced by adrenalectomy, which is especially noteworthy when one considers that it should be increased by the retardation of excretion, but it is not abolished. It seems possible that different pituitary factors, intervening in metabolism in different ways, may in varying degree tend to produce ketosis; and it is certainly not surprising that extracts which possess "diabetogenic" activity of one sort or another should also be "ketogenic" (219, 233).

Many contributions to the theory of insulin action have been made in the period under review, but there is little sign of unanimity of opinion, nor has any one aspect of the problem received especial attention. We should like, however, to draw attention to the recent statistical studies (234, 235, 236) of the assay of insulin by the rabbit method. Methods of biological assay which depend on an all-or-none, quantal response have been much studied in the past, but the theory of assay methods involving a quantitatively determined graded response has hitherto received very little attention. The chemistry and pharmacology of insulin have been reviewed elsewhere (237, 238).

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MAMMALIAN REPRODUCTIVE ORGANS

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Current investigations on the physiology of the reproductive organs are concerned primarily with endocrine interactions. The recent reviews of the endocrines by Wintersteiner & Smith and by Evans, and the preceding chapter in this volume have surveyed the field adequately. The present review is concerned principally with investigations dealing with the reproductive organs, as separate from the endocrine components. It is obvious, however, that no summary of work in the field of the physiology of reproduction can be presented without some discussion of the endocrine aspects. Actions of gonadotropic hormones are not discussed. Papers of a clinical nature are not included unless the data are quite specifically of physiological interest.

Female Genital System

Endometrium and menstruation.—There is general agreement that the conditions required to permit endometrial desquamation and menstrual bleeding are operative on withdrawal of certain hormones. The induction of bleeding in monkeys after the withdrawal of estrogens, progesterone, and, as more recently shown, of testosterone, or combinations of these substances, continue to interest investigators.

The period of latency in monkeys between cessation of treatment with estrogen and the appearance of bleeding averages 9.2 days, with extreme range of five to sixteen days. The period of latency after progesterone treatment was 2.9 days, the range being two to four days (Smith & Engle). That is, bleeding after progesterone withdrawal or corpus luteum ablation is more definitely limited in time than is the bleeding of estrogen deprivation.

In the monkey testosterone supplements progesterone in the production of a pregravid endometrium in castrates treated with hormone and in normal animals during ovulatory cycles (Hartman). In hormone-treated castrates, testosterone prevented the bleeding expected after the withdrawal of adequate doses of either estrogen or progesterone. Testosterone also maintained the

histological structure of the secretory endometrium for as long as twenty days after cessation of progesterone administration (Engle & Smith).

The prolonged action of various estrogens—estradiol benzoate, estradiol dipropionate, and triphenylethylene—in single injections was demonstrated by Engle & Crafts (1). The latency before bleeding ranges from approximately thirty to seventy days. The new synthetic estrogen of Dodds, diethyl stilbestrol, has received much attention. In monkeys its effectiveness in preventing bleeding is approximately the same whether given orally in oil or intramuscularly in oil. A single dose or injection of 20 mg. is as effective as 100 mg. or 200 mg., and is not significantly better than 2 mg. or 5 mg. [Engle & Crafts (2)]. Bishop, Boycott & Zuckerman have shown that stilbestrol induces the proliferative type of endometrium in monkeys and in women.

The orally active estrogens (stilbestrol, ethinyl-estradiol) must be absorbed from the intestine in a few hours' time, and yet are as effective for prevention of uterine bleeding as when injected intramuscularly in oily solution. This poses several interesting problems, especially in the light of the belief of Israel *et al.* and Golden & Severinghaus that the naturally occurring ovarian estrogens are altered or destroyed by the liver.

The use of pellets formed of crystalline hormones for subcutaneous implantation, the effectiveness of which was demonstrated by Deanesly & Parkes, is becoming deservedly popular and promises to come into general experimental and clinical use. Salmon, Walter & Geist have used subcutaneously implanted estrone crystals in treating menopausal disturbances and have demonstrated their value in giving prolonged and effective hormonal action.

The relation of hormone balance to the uterine threshold has been well stated by Zuckerman. He reported the case of an adolescent female castrate monkey which was injected daily with the threshold dose of 100 international units of estrone for one year. During this time the animal had eight periods of bleeding which were as uniform in interval length as are the menstrual cycles of a normal adolescent. There are at least three possibilities to be considered when attempting to explain such cyclic bleeding: (a) renal threshold (Frank); (b) uterine threshold (Zuckerman); (c) endometrial fatigue. Frank's postulate was that a cyclic varia-

tion in the renal threshold prevented the excretion of constant proportions of estrogens. Zuckerman suggests that a variation of the endometrial response to estrone constitutes a real uterine threshold, and that this variation of threshold to the available estrogen explains the cyclic appearance of uterine bleeding. On the other hand, it is clear that no organ can be constantly stimulated in all its parts without showing evidence of involution or refractoriness to stimuli.

The preceding comments on estrogens and progesterone have considered only their action on the endometrium and on bleeding latency. Determinations of the rate of urinary excretion of the estrogens in relation to the menstrual cycle are difficult to correlate with the observations made after injections of estrogens. A recent investigation of the urinary excretion of the combined estrogens during the menstrual cycle is that of Gustavson and his associates. These workers have shown great care in their technical procedures and the excretion curves may be accepted as true values for the normal cases which they studied. They find a peak of urinary estrogen excretion which occurs before mid-cycle and may be associated with ovulation. A second peak occurred about ten days later, during the presumed luteal phase. In their assays, the excretion reached zero sometimes before menstruation. They say "neither of the two peaks bears any constant relation to the time of the next menstruation, nor do they to each other." Fluhmann has made many assays on fresh blood serum of women during the normal cycle and found an increase in blood estrogens during the mid-interval and also, in several instances, a secondary rise just before or at onset of menstruation. Fluhmann has used his data and that of others to question the validity of the estrogen-withdrawal theory as applied to human menstruation. In the period immediately following menstruation, the estrogen excretion ceases or is very low, yet this period is one of intense activity in the endometrium. Likewise, the significance of the high urinary estrogen found during the presumably luteal phase is not entirely clear. It is now generally accepted that, during the menopause, the high excretion of gonadotropic substance parallels the non-reactivity of the ovary. When the ovary responds to the gonadotropic hormone of the anterior pituitary, there is little or no excretion. Interpretation of the meaning of urinary hormone assays is difficult. It is somewhat analogous to observation of the water in

a mill stream below the mill. The water can be seen rushing along, —but is it known whether it has turned the mill wheel or whether it has merely poured through the sluiceway without generating any power? Certainly it is the latter in the case of the gonadotropic hormones during the menopause.

The hormonal regulation of menstruation has been here considered as though it were a local pelvic phenomenon. Experimentally the concern may be with a menstruating uterus, but clinically the problem is the menstruating woman. The trend at the present time is toward a belief that menstruation is a general systemic and not merely a local pelvic phenomenon. Brewer has studied the fragility of peripheral capillaries, measured by the degree of vacuum required to produce capillary hemorrhage, at various stages of the menstrual cycle in normal women. He reports that capillary fragility is increased during the last few days before and on the first day of menstruation. Brewer discusses the possibility that this increased fragility is caused by a vasospasm and indicates its relation to the beginning of menstrual bleeding.

Pohle, using standard methods, has studied the blood platelet counts of thirteen normal women during a total of eighty-two menstrual cycles, no subject being studied for less than three cycles. There was in general a steady progressive decrease in the number of platelets during the fourteen days prior to menstruation, with sharp recovery on the first day of menstruation. While the sudden increase in platelet count on the first day of menstruation might be accounted for as the usual response to any hemorrhage, the steady decline of the count during the progestational phase has not yet been explained.

Hamlett has described the cycle in cebus monkeys. The cycle is sixteen to twenty days long with an average of eighteen days, with a fairly regular, postovulatory bleeding, probably menstrual in character. Ovulation was known to occur during mid-cycle at the time of maximal vaginal desquamation.

Noback studied vaginal smears of a West Coast gorilla which had been in captivity for ten years, and had had a partial bilateral paralysis of the hind limbs for three years. Menarche occurred at the beginning of the ninth year of age. Menstrual cycles ranged from 36 to 72 days, with an average length of 43 days.

From a study of the reproductive tracts of a number of platyrrhine monkeys, Dempsey concludes that in *Ateles*, ovulation ap-

pears to be completely suppressed during lactation, while in another genus, *Alouatta*, ovulation is thought to occur during lactation. Desquamation of the uterine epithelium with extravasation of blood occurs at the close of the cycle.

Metabolism of progesterone.—The recovery of pregnandiol glucuronidate from the urine of pregnant women or women in the last half of the menstrual cycle by Venning & Browne has been reviewed previously. It has been believed that the presence of the endometrium was essential for the conversion of progesterone to pregnandiol. In a preliminary report, Buxton & Westphal have shown that, in two men with Addison's disease, and in one normal man, pregnandiol glucuronidate was recovered from the urine during daily treatment with 30 mg. of progesterone. Hamblen and his associates studied the metabolism of progesterone in twenty-three patients with ovarian and menstrual disturbances. These patients were treated with estrogen and with progesterone. Endometrial biopsies and pregnandiol glucuronidate determinations were made. Some degree of progestational change was found in twenty-two of the cases, but only one showed a normal pregravid change. Uniformly, little or no pregnandiol was recovered. The authors believe that "the ineffective utilization of crystalline progesterone by the endometria of these patients seems related to an inadequate metabolism of that sterol."

The corpus luteum of ovulation has a precisely delimited life span, according to Dworzak & Berndt. Using the Magnus-Kehrer reaction on uterine strips from pseudo-pregnant rabbits, they conclude that the difference between the shortest and the longest period of functional activity of the corpus luteum is, in one race of rabbits, 7.5 hours; and, in another race, 12.5 hours.

Bioelectric phenomena and ovulation.—The original reports on the bioelectric correlates in rabbits and in women have been reviewed previously. In their most recent paper, Rock, Reboul & Snodgrass report potentiometric readings made on an additional group of women. The amplitude of the potential was comparable in all nine cases, in five of which ovulation was shown to have occurred at about the time the potential difference increased. In another, it is believed ovulation may have occurred. In three others, ovulation had not yet occurred. Since the potential differences in cases shown to have ovulated are comparable to those that had not ovulated, the authors ask " . . . . are these differ-

ences in potential caused not solely by the single event of follicle rupture, but rather by a more generalized phenomenon?" A limited number of control readings were made on three men and three women, two of whom were past the menopause, no potentiometric differences being found. It is desirable to mention the preliminary report of Barton, who was associated with Burr. Barton has studied bioelectric records of 156 menstrual cycles in 36 women, with no other test to indicate the occurrence of ovulation than the potentiometric reading. Further details regarding the possible relationship of such potentiometric readings to ovulation in woman and other physiological conditions giving similar bioelectric phenomena are awaited with interest.

Motility of the uterus and tubes.—By the use of dyes and iodochloral, Krehbiel & Carstens observed the movements of fluids in the vagina and uterus with the fluoroscope. After the introduction of the fluid into the vagina the vulva of the rabbit was stimulated. The fluids were transported to the ovarian end of the uterine cornuae within two to five minutes by movements of the vaginal and uterine musculature. Breipohl has made kymographic records of the contractions of the human uterine tubes. The material consisted of segments of 103 normal uterine tubes from women operated on for eugenic sterilization. Contractions are present at all ages in both circular and longitudinal muscle of the tube and in the mesosalpinx. These contractions are small before puberty and after the menopause. The circular muscle shows little change during the cycle, having uniformly small contractions. The longitudinal muscle shows greatest activity during the proliferative phase, gradually decreasing through the secretory phase to menstruation. In the entire tube contractions proceed from the ovarian toward the uterine end.

The important monograph of Reynolds should be consulted for further work on uterine physiology. A review by Bard, which also includes new data, regarding central nervous system mechanisms in sexual responses, with particular reference to the cat, has recently appeared. Bard shows that mating behavior in the female cat invariably has been induced by an adequate treatment with an estrogen. After removal of the cerebral cortex in cats, similar responses are released by estrogen administration, and Bard concludes that "the execution of the feline estrual behavior pattern is not dependent on any part of the cerebral cortex.

Male Genital System

Erection.—Semans & Langworthy studied the effects of faradic stimulation of the pelvic nerves of adult male cats under pentobarbital anesthesia. Stimulation of the first sacral roots gave slight erection. Stimulation of both second sacral roots caused contraction of the bladder wall and micturition, but after erection commenced, micturition was held in abeyance. Stimulation of either root resulted in a bilaterally symmetrical erection. Erection will occur on stimulation after section of both internal pudendal nerves. Stimulation of the third sacral pair gave slight erection with vesicle contraction. After constriction of the aorta, erection failed to occur after stimulation of the second sacral roots. Stimulation of sympathetic trunks and hypogastric nerves caused subsidence of erection, contraction of the ductus deferens, and emission of prostatic fluid into the prostatic urethra. Ejaculation of this fluid occurs upon stimulation of the internal pudendal nerves containing somatic, parasympathetic and sympathetic fibers. Subsidence of erection is clearly a sympathetic phenomenon.

Accessory Glands.—McKenzie and his associates have contributed a monograph with interesting and valuable data on the reproductive organs of the boar. They collected semen from boars in which the seminal vesicles or the bulbo-urethral glands or both had been removed, and after vasectomy. Observations on the volume of secretion were made. These results indicate that the seminal vesicles of the boar contribute 26 per cent of the semen volume; the bulbo-urethral glands, which are very large in the boar, contribute 19 per cent; and the testis and epididymis only 2 per cent. The prostate, which was not removed, supplies, together with the secretion from the urethral glands, about half of the total volume. It should be noted that in the boar the weight of the prostate is only about three to ten per cent of that of the seminal vesicles. The weight of the urethral glands is difficult to determine. Other methods of estimation—that is, total solids in the secretions of the various glands and glucose content—all indicate that in the boar more than one-half of the total volume is elaborated by the prostate and the urethral glands. Chemical studies of the secretions of the several glands indicate that the seminal vesicles were the source of most of the potassium, phosphorus and total nitrogen of the semen. The bulbourethral gland secretion was high in sodium, containing more than twice as much

as that of seminal vesicles, and was five times as high as blood serum of the boar. The prostate contributed most of the chlorides. It is of considerable interest that the seminal vesicles are the only source of glucose in semen, the concentration averaging 257.0 mg. per cent. Valuable data on sperm counts and on ejaculation are included in this monograph by McKenzie's group.

Gutman & Gutman (1) have reported on an active enzyme, an acid phosphatase, found in the urine and prostatic tissue of adult men, and in the blood serum of men with metastasizing carcinoma of the prostate. It is present in very small amounts in the prostates of infants and children, but in large amounts in the prostatic tissue of adult men (2). It is not present in quantity in the prostates of the mature dog, cat, rabbit, guinea pig, or rat. The preputial glands of the rat are rich in this enzyme. This enzyme is present in quantities (573 to 1,134 units per gram) in the prostates of adult monkeys, but only in traces (1 to 5 units per gram) in immature (3.5 kg.) monkeys (3). After treatment with testosterone propionate the prostate of the immature monkey was comparable to the adult in content of acid phosphatase (779 to 975 units per gram). In the monkey this enzyme is elaborated chiefly in the caudal lobe.

Farrell (1) devised a fistula of the urethra of the dog, after diverting the urine, by which the secretion of the prostate gland could be collected under various conditions. Farrell reports that in such animals there was a continuous secretion of prostatic fluid, varying from 0.2 to 1.0 cc. per hour (average, 0.3 cc.). He further considers that this product is regurgitated into the bladder. (Semans & Langworthy saw no such regurgitation.) He suggests that the prostate reacts to drugs much like the submaxillary gland, i.e., pilocarpine stimulates secretion, while atropine antagonizes pilocarpine and renders hypogastric stimulation ineffective. Stimulation of the hypogastric nerves caused an increase in prostatic secretion, but the nervus erigens failed to do so. Using this technique Farrell also reports (2) that administered alcohol is found in the prostatic secretion in concentrations slightly higher than in the blood and but little lower than in the urine.

Von Euler reports further experiments on prostaglandin, a blood pressure depressing principle obtained from the secretions of human prostate and seminal vesicles.

Martins *et al.* (1, 2) have investigated the possibility of an

endocrine control of the musculature of the ductus deferens, prostate and seminal vesicles of the rat by *in vitro* techniques. According to these investigators, spontaneous contractions are rare or absent in non-castrate rats, but in castrate rats spontaneous contractions occurred in eighty per cent of the ducti deferentes tested. These spontaneous contractions were abolished by testosterone injections, but not by estrogens. Both adrenergic and cholinergic drugs stimulated the muscles of these organs. The parasympathetic-comimetic drugs, especially pilocarpine, caused much greater reactions in the castrate than in the intact or the androgen-treated rats. The authors also investigated the response of sub-adult and adult rhesus monkeys (3). As in other species, automatic contractions of the accessory genital muscles of the monkey occurred only in untreated or estradiol-benzoate-treated castrates. Estradiol increases the spontaneous contractions of the ductus deferens and the seminal vesicle, while testosterone is inhibitory. Epinephrine, acetylcholine and nicotine excite strips of muscle both from untreated and estrogen- or androgen-treated castrate monkeys. While the muscle strips from the seminal vesicle of cats respond as described above, the ductus deferens of estrogen-treated cats, unlike the other animals studied, does not contract after the addition of epinephrine to the bath. Epinephrine so administered does cause contraction in castrates treated with testosterone (4). Strips taken from the seminal vesicle and the epididymus of men are also stimulated in a similar manner (5).

Sperm.—Heckel reported on the effect of testosterone treatment in a sixty-seven year old man. The number of spermatozoa was greatly depressed, recovering during a 73-day rest period. During a second period of treatment sperm production was again greatly reduced. Recovery to normal occurred within about forty days after cessation of treatment.

Hotchkiss *et al.* have made semen analysis on single samples from two hundred men between 20 and 36 years of age, whose wives were in the first half of pregnancy. The average volume was 3 cc. Total reducible substances averaged 306 mg. per cent with extreme ranges from 9 mg. to 810 mg. per cent (by Benedict's modification of the Folin-Wu method). The authors believe sugar determination has no clinical value. Total sperm counts ranged from 2.82 millions to 2,330 millions, with an average of 346 millions. Details of abnormal forms are also given.

McKenzie & Berliner had previously shown that whereas Hampshire rams maintained high sperm quality in both summer and winter, the Shropshire rams showed poor sperm production during the summer. Berliner & Warbritton, conducting experiments with high temperature rooms in late winter, showed that the Hampshire rams were little affected while the Shropshire rams showed almost complete destruction of the germinal epithelium. The thyroids of the latter rams were generally inactive. Thyroidectomy of Hampshire rams caused changes similar to those occurring in the intact Shropshire rams in the summer, which showed great diminution in number and quality of sperm. This deficiency was restored by adequate thyroid therapy. These authors believe that low thyroid activity causes the low sperm production of Shropshire rams in summer. Smelser has shown that thyroidectomy in rats (1) depresses sperm production, and that hyperthyroidism also causes a retardation of sperm production (2).

MacLeod reports that the metabolism of human spermatozoa in Ringer-glucose solution is almost exclusively glycolytic and not respiratory.

Effects of castration.—Teilum (1, 2), using the micro-method of Rappaport & Engelberg had reported that the blood cholesterol of man progressively increases after castration. If these observations are verified with other methods of cholesterol determination, and with proper attention to concurrent hypothyroidism or other clinical conditions, they will have considerable physiological significance. However, Kearns reports a lowered blood cholesterol in castrated men before treatment, and claims favorable therapeutic results with androgens by injection and by inunction.

Stone has shown that sexual activity of castrate rats was restored by testosterone propionate injections. In all rats the ejaculatory reflex was slower in returning than the copulatory response, and was the first to go when treatment was stopped. As measured by obstruction tests, only one of eight castrates was restored to the pre-castration level of sexual drive. Foss, who had previously reported favorable therapeutic effects from the use of androgens in a castrated man, presents further observations on the same case, using testosterone propionate by injection and inunction. His belief is that estradiol supplements the value of testosterone. Two clinical reports on the use of androgens in the treatment of hypogonadism and eunuchoidism are those of Vest

& Howard, and of Kenyon. These authors agree as to the growth of the genitalia after treatment, although only Vest & Howard claim to have found a growth in the size of the testis.

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PHARMACOLOGY

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I. THE PHARMACOLOGY OF BARBITURATES

In this review an attempt is made to cover those papers appearing in 1937 and subsequently, which, in the mind of the reviewer, are likely to be of significance in understanding the potentialities of barbituric acid derivatives. For reviews covering preceding years, the reader is referred to a summary paper by Lundy & Osterberg (1) in 1929 and by the reviewer (2) in 1939. No attempt is made to review herein the very large number of clinical papers on the subject.

Central nervous system.—Masserman (3) observed that after intravenous or intraperitoneal injections of a barbiturate such as amytal sodium, electrical stimulation of those hypothalamic regions controlling the manifestations of fear failed to elicit the usual responses. If the drug was injected directly into the hypothalamic regions, electrical stimulation was normally effective. Masserman's explanation of this phenomenon involves either the assumption (*a*) that the drug is changed after systemic absorption or (*b*) that direct injection into the hypothalamus does not present the drug to reactive tissue in an effective manner.

Hoagland *et al.* (4), in studying the effects of hypoglycemia and of pentobarbital (nembutal) on the electrical activity of the cerebral cortex and the hypothalamus of dogs, came to the conclusion that pentobarbital and hypoglycemia produce similar changes in the cortex though neither appeared to affect the hypothalamus significantly.

Bremer (5) claims that barbiturates act selectively on internuncial neurons within the cortex. This view is more or less accepted by Forbes & Morison (6). Beecher *et al.* (7, 8) observed a difference between anesthetic and hypnotic drug action in that the latter appears to affect long cord arcs somewhat analogously to high cord transection.

Rascanu *et al.* (9) found that by use of quantitative measurements of cortical activity of dogs under chloroform, barbital and

evipal, a difference exists between the effects of chloroform and the two barbiturates. Of the two barbiturates, evipal more closely simulates the effects of chloroform, due, according to the authors, to the additional alkyl group substituted on the barbituric acid ring of evipal.

Sellei & Mayer (10) observed that, as measured by the Warburg apparatus, the cerebral cortex was unaffected by evipal whereas this barbiturate had a significantly depressant action on white matter and the thalamus. These results are the reverse of those produced by anesthetics such as ether, chloroform or alcohol.

Winiwarter (11) observed that dosages of barbital, phenobarbital and evipal required to disturb placing reflexes and to produce sleep are not significantly different in decerebrate and in normal pigeons.

The concentration of barbital in the different parts of the brain, according to Keeser (12), is not uniform but is relatively higher in the thalamus and midbrain than in cortical areas.

Jowett & Quastel (13) and Jowett (14) found glucose oxidation to be depressed when brain slices are subjected to the influence of barbiturates. For purposes of comparison, it is pertinent to refer here to effects on tissues other than nervous. On liver tissue, Zorn *et al.* (15) observed that evipal and other barbiturates decreased the oxygen uptake. On the other hand, Sellei & Mayer (10) state that evipal is without effect on this activity of liver. Curiously, these authors state that liver poisoned by phosphorus develops an increased cell respiration under the influence of evipal but, under the influence of chloroform, cell respiration is decreased. Additional indirect evidence is presented by Shapiro (16) who observed a profound lowering of oxygen consumption in patients to whom amytal had been given in such doses as to produce anesthesia to the level of corneal insensitivity. This author accepts the view of Dameshek *et al.* (17) that the barbiturates depress the hypothalamus, thus interfering with the metabolism of peripheral tissues.

Respiration.—Burstein & Rovenstine (18) observed apparent hyperactivity of laryngeal reflexes, particularly involving cord adduction, following the use of ultrashort- or short-acting barbiturates such as thioethamyl, amytal, evipal, pentobarbital and pentothal. They consider this to be a manifestation of selective stimulation effected by these agents.

Lehman (19), analyzing the depressant effects of barbiturates on respiration, found stimulation of the peripheral end of the phrenic nerves to be as effective as normal in causing diaphragmatic muscle contraction; hence the depressant action must be central and not curare-like as had been postulated by earlier investigators.

Heart and arterial blood pressure.—Bouckaert & Heymans (20) have demonstrated that "somnifene," alurate, amytal, pernocton and evipal depress the proprioceptive mechanism of regulation of vasomotor tone. Heymans & Bayless (21) also have shown that while a combination of morphine and pernocton depresses arterial blood pressure, chloralosane, a non-barbiturate laboratory anesthetic, is relatively free from this liability. Nowak (22) observed that evipal produces no significant fall in arterial pressure, yet slightly depresses the carotid sinus mechanism and respiration. Amytal moderately depresses all these mechanisms while pernocton depresses arterial pressure, abolishes carotid sinus reflexes, and depresses the respiratory center. Abbate (23) recognizes the depressant action of barbiturates on the carotid sinus vasomotor mechanism and adds that hyperirritability due to pain may lead to instability of this mechanism to such an extent that barbiturates, otherwise well tolerated, may effect an excessive depression leading to collapse and respiratory paralysis. Additional evidence of altered carotid sinus activity under the action of barbiturates is found in the observations of Marri & Martinetti (24) that epinephrine becomes relatively more effective, whereas acetylcholine becomes less effective. Donatelli & Shen (25), in studying a number of drugs on the carotid sinus, came to the conclusion that picrotoxin was effective only when this mechanism had been depressed by barbiturates.

Gruber and his associates (26, 27) claim that the sulfur derivatives such as pentothal and thioethamyl are rather prone to induce cardiac arhythmia. On the other hand, Kohn & Lederer (28) found no significant changes in the EKG in dogs, cats, rabbits and monkeys following the use of pentothal. If any changes appeared they promptly disappeared at the end of the period of anesthesia. Betlach (29) also saw no significant changes in dogs. He insists, furthermore, that dogs are so apt normally to have cardiac arhythmias that months of study of individual animals must be carried out before it is possible to know whether

or not peculiarities of cardiac action under any drug might not also have occurred in its absence. In clinical practice, Volpitto & Marangoni (30) saw no deviation from the normal in seventeen carefully controlled human subjects given either evipal or pentothal. Hafkesbring & MacCalmont (31) observed that dogs and cats, subjected to the action of barbital, amytal or pentobarbital, may develop an increase in heart rate. If arhythmia was present previously, it was lessened.

Roth (32), in studying the effects of a number of hypnotic drugs on sino-atrio-ventricular preparations of hearts of the spiny dogfish, found that amytal was more depressant than paraldehyde or chloral hydrate. Hoff & Nahum (33) found that cardiac irregularities ordinarily produced by calcium could be completely prevented by use of amytal. Johnston (34) found that the depression of isolated turtle hearts produced by barbiturates was antagonized with great difficulty. Glycine or the xanthines produced this effect to some extent, whereas the central nervous system stimulants, such as coramine, metrazol or picrotoxin, were relatively ineffective.

When cardiac irregularities were produced by morphine and cyclopropane, Baxter & Robbins (35) found very small doses of amytal to be effective in correcting them, probably through simultaneous depression of the vagal mechanism as well as of the irritability of cardiac tissues. On the other hand, Melville (36) found phenobarbital, added to the perfusion fluid of the heart-lung preparation, contributed to the injury produced by posterior pituitary extracts. This was thought to be due to increased coronary constriction plus heart muscle depression.

Werner (37), in comparing pentothal with evipal in rabbits, found pentothal to be less likely than evipal to produce a fall in blood pressure when used in equivalent dosages.

Vagus.—The irritability of the cardiac vagus is significantly reduced by evipal, pentobarbital, ortal and amytal, according to Gruber, Gruber & Colosi (38), whereas the thiobarbiturates, pentothal and thioethamyl, increase vagal effects. Gruber, Haury & Gruber (39) claim that a part of the depressant action is on the post-ganglionic fibers since, after application of nicotine, electrical stimulation of these fibers is effective prior to, but not after, application of the barbiturates.

Gruber and associates (40) also reported a study of local application of different barbiturates on the exposed terrapin heart. Ortal and evipal, in M/500 solution, effect vagal block, whereas in this concentration amytal, neonal and pentobarbital produce a block in about one-half of the preparations tested. Pernocton, phanodorn, nostal and alurate require M/250 solutions, whereas in this concentration dial, ipral and barbital were ineffective.

Antagonism.—Rice & Isenberger (41) found that respiratory paralysis produced by amytal, given intracisternally in dogs, could be effectively antagonized by intracisternal injections of picrotoxin but not by coramine or metrazol. They state, however, that the failure of the latter two drugs, given as they were, does not mean that they would not be of value when given systemically. Clinically, picrotoxin has been reported to be of service in profound barbiturate depression (42, 43, 44, 45, 46, 47, 48).

Marshall *et al.* (49) consider picrotoxin to be the most effective antagonist to barbiturate depression of respiration by virtue of its decreasing narcosis rather than by specifically stimulating the respiratory center. Krantz *et al.* (50) state that the antidotal action of picrotoxin against barbiturate poisoning is not due to correction of the decreased oxygen consumption of rabbit brain tissue *in vitro* nor to change in pH values, since these remain unchanged, hence its efficacy appears to be due to some unknown mechanism termed "awakening effect." Barlow (51) speaks of picrotoxin as possessing the undesirable side action of secondary depressant effects when used as an antagonist to barbiturate poisoning. Werner & Tatum (52), however, insist that whenever such secondary depressant effects are observed, they follow convulsions produced by overdosage, and that apparently convulsions from any cause appear to be followed by depression. Hence a direct depressant after-effect of picrotoxin has not as yet been demonstrated unless the dosage be raised to the extent of producing convulsions.

Zipf *et al.* (53), in studying the antagonistic action of a number of drugs against the actions of evipal, barbital, pernocton and "eunarcon" in rats, found that metrazol was most efficient while coramine and other analeptics were considerably less effective. Picrotoxin was not included in their list of stimulants.

Kreitmair (54) confirmed the already known antagonism be-

tween phenobarbital, and strychnine, caffeine and picrotoxin. Ephedrine was found to be somewhat effective in narcotic, but not at all in lethal doses of this hypnotic.

In the line of therapeutic aids in severe experimental poisonings by barbital or phenobarbital, Cutting & Koppanyi (55) found massive intravenous infusions of glucose or saline solutions effective in diluting the drugs *in vivo* as well as aiding in elimination. For short-acting barbiturates, a stimulant analeptic was required in addition to the infusion. Simon (56), working on the antagonism between strychnine and barbital, came to the conclusion that it was based on functional antagonism and not on changes in physical or chemical states of either of the antagonists.

Fegler *et al.* (57) observed that brains of normal rabbits, of animals under dial depression, and of strychninized animals treated with dial, had essentially the same amount of acetylcholine and its precursor, while strychnine alone caused a significant decrease. These authors ascribe this decrease to the physiological responses to strychnine. Control of strychnine action by dial thus protects against this drop in amount of acetylcholine.

Zipf & Epding (58) in their study of antagonisms could see nothing but additive actions when lethal doses of an antipyretic such as pyramidon were given along with lethal doses of barbiturates. In narcotic doses of barbiturates, nontoxic doses of pyramidon had no additive effect.

Synergism.—De Nito (59) reports a potentiation of the narcotic action of magnesium and of barbital by beta-methylcholine and by ergotamine. Dille & Ahlquist (60) state that a relatively greater synergism appears between small doses of alcohol and pentobarbital than between large doses. Elimination of each drug is independent of the other. Similar results are reported by Olszycka (61).

Eichholtz & Kullmann (62) observed that while a combination of barbital with sodium salicylate produced very little analgesia in rabbits; the addition of caffeine, peculiarly, produced a definitely greater analgesic capacity. Olszycka (63) reports that simultaneous use of two barbiturates caused simple additive effects. Konzett (64) observed that fat-soluble dyes (alizarin blue S, methylene blue, neutral red) potentiated considerably the action of several hypnotics, including phenobarbital and evipal.

Relative to the question of the effect of premedication with

depressant drugs on subsequent effectiveness of anesthetic agents, Robbins *et al.* (65) make a significant confirmation of previous reports. Using cyclopropane as the anesthetic agent they find, after relatively small doses of morphine, barbital or amytal, that the blood concentration of cyclopropane required to produce the various stages of anesthesia was significantly reduced. The concentration of cyclopropane required to produce respiratory arrest did not appear to be modified by any one of these preanesthetics given in small doses. With large doses of preanesthetic depressants, the blood concentration of cyclopropane required to produce any stage of anesthesia, including respiratory arrest, was definitely reduced.

Blood.—That changes in the concentration of blood follow the administration of amytal has been reported by Higgins & Corwin (66), Searles (67), and by Bollman, Svirbely & Mann (68). These writers agree on the observations that amytal reduces the hematocrit values for erythrocytes, due largely to splenic engorgement, since splenectomy markedly reduces the relative anemia.

Urea nitrogen of blood or urine was not altered by administration of single doses of amytal to dogs, according to Gouaux *et al.* (69). Hafkesbring *et al.* (70) reported that repeated administration of pentobarbital to dogs did not significantly change either blood counts or hemoglobin readings. Similar negative results were reported by Beecher (71). These negative results stand in direct opposition to the claims of Dallemagne (72) and of de Langen (73), who maintained that anemia is easily produced in animals by hypnotic drugs. According to Mollari *et al.* (74), neither barbital nor phenobarbital produces any change in coagulability outside of the effects of concomitant alkalinity if large amounts of the alkaline sodium salts were employed. If alkalosis be avoided no change in coagulability occurs.

Clinically, a case of neutropenia from excessive use of phenobarbital was reported by Jacobson (75). Maillard & Jammet (76) reported that patients receiving phenobarbital over a period of years are subject to a significant reduction in erythrocytes. On reduction in dosage, the blood count rather promptly returned to normal.

Dyscrasias, such as purpuras, have been reported by Hill (77), by Joekes (78) and by Huber (79) following the use of the acetyl ureid of allylisopropyl barbituric acid (Sedormid). Allonal, a

mixture of amidopyrine and allylisopropyl barbituric acid, is still being reported as causing granulocytopenia, presumably due to the first named constituent (80).

Blood sugar.—Atnan & Fenz (81), in studying anesthetic agents in diabetic patients, observed that evipal administered intravenously produced practically no disturbance in blood sugar levels. In rabbits, Hrubetz & Blackberg (82) observed that amytal produced no change in blood sugar even during deep anesthesia, phenobarbital caused no change during the first hour, while seconal and pentothal effected some rise. All produced a fall of sugar level at the time of recovery from anesthesia. Epinephrine was less than normally effective as a glycogenolytic agent in animals under the influence of the above mentioned barbiturates. This diminution of effectiveness of epinephrine was thought to be due to liver damage since it occurs also in chloroform poisoning.

Smooth muscle.—Kolb & Langworthy (83), in their study of micturition, observed that pentobarbital depressed the bladder stretch reflexes such that the normally sustained vesical contraction on filling no longer occurs. In this respect pentobarbital effects simulate those produced by ether.

Gruber & Gruber (84) found that pentobarbital and evipal decreased intestinal muscle tone *in vitro* whereas thiobarbiturates produced variable results. Burstein (85) found that several short-acting barbiturates, including thio-derivatives, caused a prompt depression of rhythmic intestinal contraction and tone *in vivo*. The primary depression is succeeded by a more prolonged phase characterized by an increase in both contractions and tonus.

Chemical recovery from animal tissues.—Kozelka & Tatum (86) have analyzed the cobalt color test for barbiturates and maintain that the color produced is dependent upon two variables, namely, quantity of barbiturate and alkalinity of the reaction medium; and hence unless the approximate quantity of barbiturate is known, thus eliminating one of the variables, the reaction is not strictly appropriate for colorimetric quantitative determinations. Under certain conditions they are able to differentiate between mono- and di-imid barbiturate compounds since these two classes possess different stabilities at different pH values.

Brundage & Gruber (87) reported a method of extraction of barbiturates based on their adsorption upon activated carbon.

Kozelka *et al.* (88), however, believe that adsorption of barbiturates on activated carbon is not entirely complete.

Kozelka, Nelson & Tatum (88) described a technique for quantitative extraction, identification, and gravimetric determination of barbiturates as obtained from animal tissues. Their method involves the use of a twenty per cent aqueous solution of acetic acid as the extraction medium. Proteins are precipitated by use of tungstic acid. Subsequent extraction with ether by continuous extraction technique and final purification of the ether extract by sublimation completes the process. They observed that morphine as a premedication agent and carbon tetrachloride as a tissue poison significantly retard the destruction *in vivo* of amytal, chosen as a representative of the destructible barbiturates. These quantitative results based on chemical recovery confirm, in a chemical way, inferences reported by Cameron & de Saram (89), and by others earlier, that liver injury interferes with destruction *in vivo* of barbiturates.

Cerebrospinal fluid.—Kozelka & Tatum (90) were unable to find significant amounts of the barbiturate in the cerebrospinal fluid after administration of rather large doses of phenobarbital or other barbiturates. By pooling the fluids of a number of human patients, they were able to isolate and identify a milligram of barbiturate from a liter of the pooled fluids. Controlled tests made on fluids free from barbiturates, and to which known amounts of a barbiturate were added, prove the adequacy of their technique. These results are in sharp contrast to certain previous claims that barbiturates are secreted in large proportions into the cerebrospinal fluid.

Tolerance.—In the experimental field most investigators find clear-cut evidence of a partial tolerance. Ettinger (91) reported a marked tolerance developed in dogs which had received dial. Pentobarbital, according to him, produced the greatest duration of action on the first administration but after the third dose the duration of effect was constant but shorter than that produced by the first dose. Moir (92) reported that rats developed a tolerance to pentobarbital. Masuda *et al.* (93) reported tolerance development on repeated administration of amytal, pentobarbital and pernocton, but not with ortal or evipal. Carmichael & Posey (94) found pentobarbital to produce a tolerance in guinea pigs.

Oettel & Krautwald (95), working with dogs, observed that barbital and phenobarbital produced a degree of tolerance in that the duration and depth of depression became less on daily repetition of dosage. Marked increase of reflex excitability was observed during the course. In contrast to morphine, these symptoms of hyperirritability were not exaggerated on withdrawal of the drug. Phanodorn caused the development of a tolerance of such a degree that the dosage had to be increased from 75 mg. per kg. up to 130 mg. per kg. Rate of excretion of the drug was observed to have increased but there was no change in rate of destruction. Nostal produced a remarkably rapid development of tolerance. Initially, 50 mg. per kg. caused a sleep for six to seven hours with distinct increase in reflex irritability. After a few days, 75 to 90 mg. per kg. caused no sleep and scarcely any narcotic effect. Increase in dosage up to 196 mg. per kg. resulted in sleep for a few hours. By continued use of this high dosage, tolerance continued to appear. No abstinence symptoms were observed on withdrawal. An increase in rate of destruction of nostal occurred, a finding in contrast to other barbiturates studied. All the barbiturates tested led to a condition of lessened susceptibility of the nervous system. Thus, barbiturates appear to resemble the effects of alcohol addiction rather than morphine addiction since true abstinence symptoms were not observed.

In clinical practice, Robinson (96) states that the development of tolerance, while not as marked as with opiates, nevertheless leads the "barbital addict" to take larger and larger doses so that the patient is soon taking toxic doses, which not only produce the clinical evidence of toxicity but also pathological changes in the brain. The author holds that there exists a strong psychogenic factor in any kind of drug addiction.

Schmidt (97) states that, in eleven cases of epilepsy having received phenobarbital for six or more years, withdrawal symptoms appeared in each case, both in respect to the epilepsy and also to the circulatory system. Five showed definite improvement after a few days and no longer required the drug. The other six patients did not improve and were returned to their regular dose of phenobarbital. In contrast to all these reports, Swanson *et al.* (98) saw no evidence of tolerance development in dogs or monkeys receiving amytal over a period of several months.

Sex susceptibility.—Holck *et al.* (99, 100) found definite differ-

ences in susceptibility in male in comparison to female rats towards short-acting barbiturates but no differences when long-acting barbiturates were used. In the mouse, guinea pig, rabbit, cat and dog, no differences in susceptibility appeared between the sexes. On repeated administration, Moir (92) found young female rats to be more resistant than young males. Mature female rats were found to be less resistant than mature males. Carmichael (101), on the other hand, found no change in the median lethal dose of pentobarbital referable to sex of rats though young rats were more resistant than old animals.

Acute toxicity, "accumulation," and detoxication.—Sweitzer & Laymon (102) and Novy (103) have called attention to skin eruptions due to barbiturates. Novy observed a case sensitive to amytal. This patient appeared to be sensitive only to barbiturates having an ethyl group in position *5*. This is taken to mean that sensitivity may be so highly specific that even closely related compounds may be ineffective in provoking sensitivity reactions. Schulte (104) failed to obtain any evidence of tissue changes in skin, liver, kidney, spleen or heart muscle in rats or dogs subjected to barbiturates throughout a period of one hundred days for rats and two hundred days for dogs.

According to Gruhzit *et al.* (105), the thiobarbituric acid derivatives are especially prone to produce congestion, stasis, and hemorrhage in the lungs, liver, kidneys, and the central nervous system when administered in anesthetic doses to laboratory animals. No clinical reports in which correspondingly pathological sequelae were observed have come to the reviewer's attention.

Reynolds & Veal (106) state that pentothal in moderate overdosage leads to cessation of respiration. On continued administration of the drug in a dosage just adequate to maintain light anesthesia, signs of heart muscle poisoning may appear without warning. They conclude that regardless of care in administration, the longer the duration, the greater the danger of circulatory failure. In another contribution, these authors (107) report the development of acute cumulative phenomena. The first dose produces a period of anesthesia lasting for a few minutes. Subsequent administrations given before complete recovery lead to progressively longer periods of depression indicating that the drug is cumulative, i.e., not rapidly and completely destroyed, as might be inferred from the short period of depression on the initial injection. Ko-

zelka & Hine (108) have confirmed the observations of Reynolds & Veal and have studied chemically the fate of pentothal in the body. They were unable to demonstrate pentothal in tissues after a lapse of approximately ten minutes. After repeated administrations a very prolonged period of depression resulted. In even profound depression lasting for hours, they were unable to demonstrate either pentothal or its oxygen analogue, pentobarbital, in body tissues. Had these animals received pentobarbital in quantities sufficient to produce a similar grade of depression, no difficulty whatsoever would occur in demonstrating this drug. Therefore, these authors are forced to conclude that pentothal produces its cumulative effects through accumulation of some unrecognized degradation product.

In contrast to pentothal, Butler & Bush (109) find that N-alkyl derivatives of long-acting barbituric acids, e.g., N-methyl barbital or N-methyl phenobarbital, are to a large extent transformed by demethylation into the nonmethylated or original barbiturate. In instances of N-methyl derivatives of short-acting barbiturates, as in narconumal (N-methyl alurate), demethylation does not appear to be a very important factor since these substances are readily destroyed by other mechanisms (110).

II. THE PHARMACOLOGY OF ARSENICALS

This review of arsenical preparations presents no claim for completeness. It does include, however, reference to those papers which offer concepts of considerable importance, and from which a reader may readily gain access to a more complete bibliography of the various phases of work in this field.

Blood.—Oelkers (111), in studying the action of arsenic as a tissue poison, concluded that its effects are to inhibit or depress protease, cathepsin, lipase, and also cell respiration. Changes in the endothelium can well be explained as being secondary to these changes in enzymatic activity. In another study (112), this author demonstrated that intravenously injected dextrose disappeared from the blood more slowly in acute arsenic intoxication than in normal control experiments. Arsenic also caused a prolongation in the action of epinephrine as a glycogenolytic agent and a more prolonged hypoglycemia on administration of insulin. Both of these actions indicate a significant disturbance in mechanisms that control sugar mobilization.

In clinical practice, several observers reported blood dyscrasias, including aplastic anemia, granulocytopenia, and thrombocytopenia, subsequent to the use of arsphenamine or neoarsphenamine (113 to 121).

Lymphatic system.—Bertschinger (122) observed that after repeated small doses, or after single large doses, of inorganic arsenic given to rabbits, there occurred a well-marked lymphopenia. Since a microscopic examination of liver tissue revealed an equal or corresponding reduction in the concentration of lymphocytes in that organ and since it would be improbable that aggregation could occur elsewhere without being evident also in the liver, the author concludes that lymph cells must have been destroyed by arsenic within the blood stream.

Heart.—Akita & Kondo (123) studied, by means of the electrocardiograph, the toxic action of the arsphenamines on the rabbit heart. They observed that oxidation of the arsphenamines produced an expected increase in toxicity.

Tanzi (124) investigated the action of various substances on the toxic effects of atoxyl on the perfused rabbit heart. He found

that alanine and tyrosine were each definitely protective, whereas glycine and cystine as well as glycerol were without effect.

Liver.—The effect of arsenic on the enzymes of the liver has been the subject of study by several investigators. Lightbody & Calvery (125) have found that the arginase content of the liver is reduced in rats receiving arsenic directly, as is also the case indirectly in the young which are suckling those mothers which are receiving arsenic.

Lamb & Blakely (114) observed that neoarsphenamine raises the phosphatase content of plasma; this increase precedes the rise of the icteric index, hence may be a means of early detection of liver damage. Maver & Voegtlin (126) however, found that arsenates inhibit phosphatase in its action on sodium glycerophosphate. These authors also observed that arsenate inhibits the action of nuclease on nucleic acid in tumor, thymus, and liver tissue.

Von Glahn *et al.* (127), in studying the action of arsenate on the liver of rabbits, found that animals that had received a diet rich in carbohydrates developed less necrosis and cirrhosis than animals on a low carbohydrate diet. A high glycogen content of the liver was somewhat protective against the toxic action of arsenic. These observations stand in opposition to a report in the older literature of a somewhat analogous study in the dog, in which Craven (128) found a high carbohydrate diet conducive to an increased susceptibility to liver poisoning by arsphenamine, whereas a diet low in carbohydrate but high in protein and fat reduced the susceptibility to poisoning by this arsenical preparation.

Moxon (129) reported that selenium was a very potent liver poison when administered to rats as seleniferous grain. When, however, a small amount of arsenic was administered simultaneously with the seleniferous grain, the latter ceased to be toxic.

Soffer *et al.* (130) produced jaundice in a series of dogs by the use of arsphenamines. The degree of poisoning resulting in jaundice caused death of the majority of the animals. In addition to severe central necrosis of the liver and tubular nephritis, the blood presented marked changes, such as increases in potassium, lactic acid, and phosphate, and decreases in chloride and carbonate content.

In a study of the records of a large series of patients receiving arsphenamines, Soffer (131) reported that 0.87 per cent developed

jaundice. Arsphenamine produced jaundice one and one-half times as frequently as did neoarsphenamine.

Thyroid.—Kampelmann (132) observed that small doses of inorganic arsenic led to a decrease in activity of the thyroid gland, as indicated by flattening of epithelial cells and increase in volume of colloid within acini. The author suggests that this evident decrease in thyroid activity is basic to the increase in body weight so frequently observed clinically. The mechanism of action, according to this investigator, is that the arsenic decreases the rate of secretion by the hypophysis of the thyroid-stimulating hormone.

Optic nerve.—Fine & Barkan (133), Mayer (134), Moore *et al.* (135) have reported summary studies on the clinical evidence of optic atrophy following the use of tryparsamide in neurosyphilis. Their general views are expressed by Fine & Barkan who conclude that though a hazard exists, the continued clinical use is justified by the proved therapeutic value.

Distribution and excretion of arsenic.—Distribution of arsenic in the body of the rabbit following intravenous administration has been investigated by Richter (136) and by Kraft *et al.* (137), and following chronic poisoning, by Calvery and associates (138). Excretion of arsenic when administered in the inorganic form is, according to Orestano & Abbate (139), almost entirely by way of the kidneys, while organic arsenicals, especially of the trivalent group, are excreted by way of both the bowel and the kidneys. Hove *et al.* (140) reported that in normal rats eighty per cent of ingested inorganic arsenic is to be found in erythrocytes.

Pregnancy.—That pregnancy in syphilitic women constitutes a serious problem for the therapeutist is pointed out clearly by Ingraham (141). This author, after an extensive survey, calls attention to many complications resulting from the use of the arsphenamines and states that the percentage incidence of reactions due to treatment is higher than in a similar number of non-pregnant women.

The question of whether or not arsenicals pass through the placenta into fetal tissues has been studied by several workers. Snyder & Speert (142) observed that when neoarsphenamine was given to the pregnant rabbit, the arsenic content of the fetuses increased as term approached, indicating a freer passage in the second half of the pregnancy period. At term, the concentration

in the fetuses approached that of the maternal tissues. Morris *et al.* (143) found that after administration of inorganic arsenic to pregnant rats, arsenic was found in the tissues of the newborn. They also demonstrated that rapidly growing tissues absorbed arsenic to a greater extent than do slowly growing tissues. These results of experimentation are fairly paralleled by observations of Konschegg *et al.* (144) who found that the fetus obtained from a pregnant woman dying of arsenic poisoning contained a greater concentration of arsenic than did the maternal tissues. It is interesting to note that in this instance arsenic was administered by way of the vagina, thus proving that arsenic may be absorbed in toxic quantities when so administered.

Vamos & Böhm (145) reported an instance of fatality following arsphenamine therapy of a pregnant woman. The maternal tissues, the decidual vessels, and the intervillous spaces contained arsenic, but the chorion and fetal tissues contained no arsenic. The author did not give the fetal age.

Adjuvants and derivatives.—A considerable amount of study has been devoted to the problem of reduction of toxicity of the arsenobenzenes. Strangeways (146) reported that glutathione diminishes considerably the toxic action of arsenoxides providing it is used in large excess. Owing to the fact that efficiency is retained, the author assumed that a free dissociation of the complex can occur in the absence of an excess of glutathione. Versari (147) and Lambert (148) both claimed that a significant reduction of toxicity of the arsphenamines occurred when they were dissolved in solutions of glycine. Shaw (149) found that decholin reduced greatly the clinical reactions produced by neoarsphenamine. Risi (150) employed the mono-iodohydrate of hexamethylenetetramine as an adjuvant to neoarsphenamine and reported a marked reduction of undesirable clinical reactions and an actual rise in the therapeutic index of the arsphenamines in rabbit syphilis. Jurist & Christiansen (151) claimed that cystine added to neoarsphenamine produced no change in toxicity, yet it did reduce trypanocidal effectiveness and consequently could not be considered feasible for clinical purposes.

Eagle (152), studying this general problem by *in vitro* technique, came to the conclusion that cysteine, glutathione, and thioglycollic acid markedly reduced the spirocheticidal effectiveness of arsenicals. He, as did others, assumed a dissociation *in vivo*, thus accounting for therapeutic efficacy.

Sensitivity.—Studies of the nature of sensitivity to certain arsenicals have been made by a number of investigators. Cormia (153) and Dainow (154) have reported that vitamin C is an effective preventative. Dainow believes that the more or less successful utility of atropine and of epinephrine implicates the autonomic nervous system. Furthermore, he considers vitamin C to have a definite regulatory control over this system. Landfisch (155) and Friend & Marquis (156) have contributed significant clinical evidence of the protective value of vitamin C.

Miesscher & Schnitzer (157), on the basis of their work on guinea pigs, believe that the quality of precipitating sensitivity reactions is more or less immediately dependent upon free amino groups of arsenobenzene compounds. French investigators [Tzanck & Lewi (158) and Rivalier (159)] have made intensive studies of mechanisms. While they are not in entire accord in all phases, they agree in ascribing to the autonomic nervous system an important mediate role. Rivalier *et al.* (160) have demonstrated that the injection of an active arsenical (sulfarsphenamine) into a ligated blood-free vein of a sensitized animal precipitates a definite reaction. This reaction involves an effective stimulation of sensory nerves in the venous walls which reflexly affects the autonomic nervous system, viz., to increase parasympathetic and decrease sympathetic nerve actions and tonicity. Thus, a considerable part of the sensitivity reactions, e.g., nitritoid crises, appear to be due to reflex nervous mediation. Flocculation reactions may or may not occur as an accessory phenomenon but are not necessary to the reaction since the crises may occur in the absence of demonstrable flocculation.

Astrachan & Sharp (161) reported considerable clinical success in the use of liver extracts in instances of arsenic sensitivity other than those developing exfoliative dermatitis. On the other hand, Epstein (162) reported negative results.

Tolerance development.—Kuhs *et al.* (163) observed the effects of different types of organic arsenical preparations given repeatedly to different species of laboratory animals. A number of arsenicals, viz., acetarsone, carbarsone, tryparsamide, and maph-arsen, developed a well-marked tolerance, some up to twice the usual minimal lethal dose, whereas others, such as neoarsphenamine, sodium cacodylate, and sodium arsenite, given throughout a corresponding period, produced no evident tolerance. In order to produce a tolerance, with the tolerance-producing

members of the series, it appeared necessary to administer the drugs in quantities sufficient to produce some tissue damage; otherwise tolerance, as indicated by final tests, was not developed. The nature of the tolerance development was not established.

Arsenic-fastness.—Arsphenamine-resistant syphilis continues to be observed by clinicians, as indicated in recent papers by Netherton (164) and by Beckh & Kulchar (165). In both papers instances are cited in which arseno-resistance could not have been due either to differences in the drug or to any specific variation in the strain of spirochete. Hence, the responsibility for the arsenic resistance appeared to be a function of differences in the hosts.

Lisi (166) administered small repeated doses of arsphenamine for several weeks prior to the inoculation of spirochetes into rabbits. The course of the disease was then followed both with and without ordinarily adequate therapy. There was observed in the treated series a reduction in the growth and development of lesions but there was clearly a lessened efficiency of therapy when compared with a control series which did not receive arsenic prior to inoculation. The author believes that the differences are to be explained on the basis of changes in the reacting capacity of the substrate and not to an assumed arsenic resistance on the part of the parasite.

Bovet & Montezin (167) observed that different arsenical derivatives possess different capacities to produce arsenic-fastness in trypanosomes. There appeared to be no relationship between the capacity to produce arsenic-fastness and the therapeutic index. Hawking (168) presented evidence that arsenic-resistant trypanosomes developed a refractoriness towards absorption, hence arsenic-resistance appeared to be due to decreased affinity.

Tests for activity.—Morrell *et al.* (169) proposed a test particularly applicable to comparisons of different brands and lots of neoarsphenamine. The method consists in the use, as test animals, of rats infected with *Trypanosoma equiperdum* and the determination of the minimal quantity of drug which will clear the blood stream of trypanosomes in a period of five hours. Bülbring & Burn (170) used mice infected with *T. equiperdum* as test animals and depended upon the determination of that dosage which leads to a seven-day survival of the animals.

Hawking *et al.* (171, 172), in attempting to evaluate arsenical and other compounds, made a study of the arsenic content and

the trypanocidal capacity, *in vitro*, of human cerebrospinal fluids from individuals receiving these materials by intravenous injections.

Eagle (173) has applied various drugs to suspensions *in vitro* of spirochetes and noted the concentration of drugs and time of exposure required to inhibit movement and to abolish infectivity.

In treating trypanosomal infections in various laboratory animals, Longley *et al.* (174) found that therapeutic responses in hosts of different species varied greatly. Certain compounds which possessed remarkably high therapeutic indices for *T. equiperdum* infections in rats were practically valueless for *T. evansi* or *T. hippicum* infections in rabbits or dogs. Conversely, certain compounds which rated lower in *T. equiperdum* infections in rats headed the list effective in *T. evansi* or *T. hippicum* infections in rabbits or dogs. The authors, therefore, concluded that testing arsenical compounds on one species of host infected by one species of trypanosomes gave but a very limited assay of drug potentialities.

Bovet & Montezin (167) observed differences in the capacity of different arsenicals to produce arsenic-fastness and hence believe that such information should be obtained in connection with other tests such as therapeutic indices.

Specific Chemotherapy

The scope of this review scarcely permits of an analysis of the many papers on various subjects pertinent to this subtopic; consequently this important phase is presented with extreme brevity.

Bacteriostatic action.—Several arsenic analogues of some of the sulfone derivatives have been studied by Rosenthal *et al.* (175). While certain of these analogues have some bacteriostatic activity, they do not compare very favorably with certain other sulfone derivatives.

Blackhead of turkeys.—Blount (176) reported success in the use of "mapharside" in this disease and recommended it on account of its relative safety and efficiency.

Dysentery.—Hakansson (177) presented a recent report on the effectiveness of carbarsone in clinical amebiasis. Of fifty-three patients who received this drug, twenty were cured, i.e., follow-up tests for one year gave negative results. Given orally, it is relatively nontoxic. Van Wesel (178) employed neoarsphenamine

along with other agents and claimed to have obtained better results than when this arsenical was not used.

Giardia infection in rats.—Armaghan (179) reported "Aldarsone" to be highly giardicidal and relatively nontoxic. Administration of this drug in the middle of a four-day observation period failed to remove the infection from only one of 125 rats.

Malaria.—Studies in the therapy of therapeutic and naturally acquired malaria by mapharsen were reported by Goldman (180) and by Cleveland & Turvey (181). This arsenical proved to be more satisfactory clinically than quinine in benign tertian malaria on account of its efficiency and freedom from untoward side actions. In quartan malaria, Young & McLendon (182) state that whereas this drug relieves the symptoms, it does not eradicate the infection.

Syphilis.—This subject may be subdivided into phases, viz., (*a*) early syphilis, (*b*) congenital syphilis, (*c*) latent syphilis, and (*d*) neurosyphilis.

(*a*) In early syphilis considerable interest is shown in the use of mapharsen on account of its effectiveness, coupled with a remarkable freedom from seriously deleterious side actions which are so frequently seen with the arsphenamines [Chargin *et al.* (183), Rajam & Rao (184), Lane (185) Nudemberg & Garros (186), Goldberg (119), Cornell & Astrachan (187), and many others]. A contribution by Appel (188) is of particular interest: In a series of twenty-eight patients having cardiovascular syphilis, a condition well known to constitute a serious therapeutic hazard, he reported complete absence of any undesirable reactions in twenty-one patients, while marked clinical improvement occurred. This record is worthy of special note.

In connection with methods of administration, attention should be called to the massive dose therapy by the continuous intravenous drip method advocated by Hyman *et al.* (189). These investigators found that by this technique very large total doses could be administered in a relatively short period of time. The frequency of reactions and the limited experience caused the authors to be quite hesitant in drawing any final conclusions as to the practical efficacy of the technique.

(*b*) Relatively successful use of mapharsen in the treatment of congenital syphilis has been reported by Cornell & Astrachan (187), Morgan (190), and Howles (191). Acetarsone ("Stovarsol") con-

tinues to be of interest in this phase of the disease, as made evident by papers such as those by Rosenbaum (192), Sézary & Barbé (193), Smith *et al.* (194), Lyon *et al.* (195) and Pillsbury & Perlman (196). Clinical toxicity of this substance was reported by Worms (197). In one instance, a previously sensitized patient responded to acetarsone by a nearly fatal crisis. Roubier (198) reported an instance of bilateral cubital palsy resulting from its clinical use. Experimentally, Rosahn & Kemp (199) decided that in rabbit syphilis, which represents a more acute phase of the disease, acetarsone is entirely unreliable on account of its toxicity, when given orally. Confirmatory data on this point were reported by Tomita (200).

(*c*) In the treatment of asymptomatic or latent syphilis, Astrachan & Wise (201) stressed the advisability of selecting antisyphilitic agents which, while possessing established efficacy, are at the same time least likely to produce undesirable side actions. They found mapharsen to be the arsenical agent most nearly meeting these requirements.

For similar reasons, Smith (202) and Phillips & Knoepp (203) employed mapharsen in the treatment of syphilis when it was found as a complication in tuberculous patients, as did Bittinger (204) and Goldberg (119) in instances of syphilis in pregnant women. Castallo *et al.* (205) presented a dissenting view in that, in their series, a higher percentage of babies born alive were syphilitic than where neoarsphenamine was employed. On the other hand, this report must be read in conjunction with that of Ingraham (141) who stressed the point that not infrequently serious complications arise from the use of arsphenamines.

(*d*) In the treatment of neurosyphilis four arsenicals may be mentioned,—acetarsone, mapharsen, "drug 190," and tryparsamide.

Sézary & Barbé (193) reported on their experience with acetarsone during the preceding fifteen years. They believe that this drug has proven to be as effective as therapeutic malaria and less dangerous to patients. If the syphilitic focus is located outside of the central nervous system, the drug has little, if any, effect. Pakenham-Walsh & Rennie (206) treated twenty-two cases of paresis with acetarsone and obtained results warranting further trial.

Bennett & Lewis (207) combined artificial fever with chemo-

therapy, using mapharsen as the drug; the basis for this treatment was the employment of an active spirocheticide along with a metabolism-disturbing agency such as fever. Favorable results were reported.

Tatum *et al.* (208) reported the use of a new arsenical in which the amine side-chain occupies the meta position relative to the arsonic acid in contrast to atoxyl derivatives, such as tryparsamide, in which the nitrogen is in the para position. In a representative series of cases, this chemical was found to be quite effective in any stage of syphilis, including neurosyphilis, but unfortunately possessed the property, similar to tryparsamide, of producing optic nerve disturbances.

Tryparsamide continues to be, generally speaking, the drug most frequently employed. Attention has been focused, to a considerable extent, upon complications such as injury to the optic nerve. The reader is referred to publications on this subject by Muncy (209), Fine & Barkan (133), Mayer (134), Moore and associates (135) and to a recent editorial (210). These investigators claim that optic nerve injury can be avoided in most cases by careful clinical observation and by prompt cessation of treatment for a few weeks at the first appearance of signs of damage.

Regarding systemic intoxication, Traenkle & Dolce (211) reported two instances of acutely fatal liver necrosis, apparently due to the use of tryparsamide.

Trichomonas infestation in rats.—Nelson & Tatum (212) and Rakoff (213) reported studies on the comparative efficiency of a number of organic arsenical preparations which appear to be much superior to nonarsenic-containing substances.

Trypanosomiasis of man.—Pearce (214) reported a statistical study of results of the use of tryparsamide in the treatment of human infection by *T. gambiense* in Africa. Up to the present time, tryparsamide is the only drug known to be effective in both early and late phases of this widespread disease.

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DEPARTMENT OF PHARMACOLOGY AND TOXICOLOGY
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DEFENSE MECHANISMS IN INFECTIOUS AND RELATED DISEASES

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Both non-specific and specific mechanisms play a part in the defense against infectious disease. The former are concerned with the varying structural and functional characteristics of cells and tissues and the latter with the formation of specific antibodies and the altered reactivity of tissues. Because of limitations of space, emphasis in this review will be on general mechanisms, and problems of specific diseases will be considered only as they are related to those of infectious disease as a whole. It is obvious, also, that many important contributions cannot be discussed in detail; only those will be cited which appertain to functional aspects of immunology. It would be impossible, otherwise, to survey even slightly the large number of papers published in the year 1938 alone.

Non-Specific Mechanisms of Defense

Non-specific natural resistance serves either to restrain the growth and spread of infectious agents or to augment and make more effective the cellular and tissue reactions against them. Thus, the degree of maturity of tissues, hormonal and nutritional influences, heredity and environment, structural and functional integrity of epithelium and of other limiting membranes, and inflammation, may all influence materially the chances of successful parasitism.

Influence of age.—The influence of age on susceptibility and resistance is well known, as is illustrated by those diseases characteristic of childhood, midlife and old age. It is a well established fact that young animals, as a rule, react less favorably than older ones to cutaneous infection and to chemical irritation; young animals also form specific antibodies less readily. Several recent papers substantiate these statements. Orskov & Andersen (1) have observed that young animals are less resistant than older ones to smallpox virus and react less vigorously to its cutaneous injection. Traub (2) has shown that the virus of choriomeningitis, after

natural infection, persists longer in young than in older mice and causes a severer infection in the former. Sabin & Olitsky (3) have demonstrated that young mice are susceptible to the peripheral inoculation of the virus of vesicular stomatitis whereas old mice are resistant. They have found also that in the latter the virus neither involves terminal processes and cell bodies of neurons nor spreads to other neurons, these facts suggesting that the ability of the virus to spread depends upon the state of maturity of the tissues. Thompson & Dubos (4) have shown that experimental osteomyelitis, produced by the intravenous injection of bacteria, occurs more readily in young rabbits, due presumably to the greater vascularity of the growing metaphyses. Culbertson (5), in attempting to explain the greater susceptibility of young animals to certain kinds of infections, has shown, by intravenous injection of solutions of trypan blue into rats of different ages, that the Kupffer cells of nursling animals are much less actively phagocytic than are those of older animals. He has suggested, therefore, that the resistance of older rats to infection with *Trypanosoma lewisi* may be due to the greater phagocytic capacity of their reticulo-endothelial cells. Hertzog (6) has demonstrated a definite relationship between maturity of polymorphonuclear leukocytes and phagocytic ability in that mature leukocytes were actively phagocytic whereas myelocytes and myeloblasts were but slightly so.

Barrier-action of living membranes.—The barrier-action of epithelium is illustrated by the experiments of Gordon & Lennette (7) in that, after introduction of the virus of poliomyelitis into the nostrils of rhesus monkeys, they were unable to demonstrate its passage into the blood. Schulz, Warren & Drinker (8) found the mucosa of the nasopharynx similarly impermeable to the passage of non-virulent bacteria and suspensions of India ink, whereas virulent microorganisms penetrated it readily and were demonstrated in the cervical lymph. Important information has been secured within recent years concerning the resistance of vaginal epithelium. This epithelium, although ordinarily highly resistant to infection, is more susceptible in infancy and after the menopause. It is now evident that its resistance depends to a large extent upon the action of estrogenic hormone (9, 10, 11, 12, 13). During the active sex period this epithelium is many cell layers thick, is rich in glycogen, has an acid reaction and a bacterial

flora dominated by aciduric types of microorganisms (Doederlein's bacilli). In this environment the usual potentially pathogenic bacteria cannot easily become established. In infancy, however, when this epithelium is thin and the cells are poor in glycogen, gonococcal vaginitis not infrequently occurs. Similarly, after the menopause, when the atrophic vaginal epithelium becomes poor in glycogen, and the reaction becomes less acid and a mixed type of bacterial flora predominates, so-called senile vaginitis may develop. Several groups of workers have shown that in these two conditions the administration of estrogenic substance, by parenteral injection or in vaginal suppositories, may restore the epithelium to its glycogen-rich state with elimination of the gonococci in gonococcal vaginitis and improvement of symptoms in senile vaginitis. The general hormonal effects in the former type of infection are apparently temporary and have not seemed to cause any permanent harm, so far as can be ascertained at the present time.

The question of the variations in permeability of membranes within the body, particularly of the endothelial lining of blood and lymphatic vessels and the pia-arachnoid membranes, is also receiving more attention. The many infections of nervous tissues by viruses of various sorts have aroused interest especially in the so-called blood-brain barrier. Lennette & Reames (14), and Lennette & Campbell (15, 16) have shown that the permeability of this barrier is definitely increased in the acute stage of experimental poliomyelitis in rhesus monkeys. Sohier, Jaulnes & Buvat (17) have demonstrated that tetanus and diphtheria antitoxins are able to pass across the meningovascular barrier and appear in the spinal fluid, although in lower titer than in the blood. They showed, also, that in some instances cerebral lesions increased its permeability. Kempf, Nungester & Soule (18) have found, however, that in monkeys infected with poliomyelitis, only a small amount of antiserum in the blood passes into the spinal fluid. Such findings question the value of serum therapy in infections of the nervous system. The action of the pia-arachnoid as a mechanical barrier is also demonstrated in the experiments of Howe & Peele (19), in which no apparent disease resulted after poliomyelitic virus was allowed to drip onto the exposed cerebral cortex of monkeys. If, however, pial injury was produced, paralysis resulted. Friedemann and associates (20) have proved that the

cerebral capillaries of the guinea pig and rabbit are permeable to antibodies, in opposition to the view that the difficulty in passive immunization against the viruses of poliomyelitis, rabies, and herpes is due to the natural impermeability of these capillaries. The possible influence of molecular size is suggested by the findings of Yoffey, Sullivan & Drinker (21) that egg albumen, when placed in the nose of cats, dogs, monkeys and a rabbit, entered the cervical lymph whereas horse serum did not. Bennett & Shaffer (22) have shown similarly that egg albumin injected into the blood of rabbits appeared in the synovial fluid sooner than did horse serum. McMaster & Parsons (23) have injected vital dyes into the lymphatic vessels of the ears in living mice and have seen the dye pass into the surrounding tissues along definite channels in the connective tissue. After irritation with xylol, however, the dye passed through the lymphatic walls as a diffuse cloud, illustrating the effects of injury in causing increased permeability. A decreased permeability of lymphatic endothelium for the passage of pontamine sky blue is indicated, on the other hand, by the experiments of Joyner & Sabin (24) in which its spread was restricted when the dye was injected into the skin of guinea pigs allergic to tuberculin.

Inflammation.—The importance of inflammation as a defensive mechanism is generally recognized although inflammation alone, even if intensified, may be powerless at times to prevent the spread of highly virulent microorganisms (25). The reaction may be interfered with also because of the liberation by bacteria of so-called negatively chemotropic substances which repel leukocytic accumulation. The idea of negative chemotropism has been difficult to prove, but recently McCutcheon, Coman & Dixon (26) have demonstrated its existence by observing on a glass slide the repulsion of leukocytes mixed with kaolin or with a specific strain of beta hemolytic streptococcus. They suggested, therefore, that a deficient chemotropic reaction may explain the unfavorable leukocytic response in some types of streptococcic infection. Pickrell (27) has shown that the inflammatory reaction may be paralyzed as a consequence of severe alcoholic intoxication or of ether or avertin anesthesia. Under such conditions rabbits passively immune to pneumococci succumbed to cutaneous infection, due to an inhibition of the vascular inflammatory response as evidenced by the absence of capillary dilatation and leukocytic

migration and by the uninterrupted growth and spread of pneumococci to the body as a whole. The varying phases of the inflammatory reaction itself offer intriguing problems. Menkin (28, 29, 30) has reported additional studies indicating the presence, in areas of acute inflammation, of a substance which increases capillary permeability and induces leukocytic migration. This substance is a crystalline nitrogenous material which he has named leukotaxine. He believes, contrary to Bier & Rocha e Silva (31), that it is not histamine. Menkin has also isolated a leukocytosis-promoting factor from inflammatory exudates which plays a part in the mechanism of inflammatory fixation. Miller (32) has found that, although the inflammatory reaction tends to retard the absorption of indiffusible protein, carbohydrates and dyes, it accelerates the absorption of diffusible carbohydrates and dyes. The importance of phagocytes in inflammation is illustrated by the experiments of Lawrence, Pearse & Mider (33). These workers made guinea pigs neutropenic by injection of an antileukocytic serum and then infected experimental wounds with living virulent staphylococci. A diffuse cellulitis occurred, in contrast to the development of a localized suppuration in the control animals. The importance of monocytes as defensive agents is suggested by the experiments of Pullinger (34) in which the simultaneous injection into guinea pigs of *Bact. monocytogenes* and *Alcaligenes abortus* induced a monocytosis coincident with an enhanced resistance to the infection with the latter organism. Conway (35, 36) has shown, in infections of rabbits with *Bact. monocytogenes*, that the monocytes develop from preexisting lymphocytes and from lymphocytes which are formed in the lymphatic nodules and the periarterial lymphatic splenic tissues. She has demonstrated that during the initial stage of hyperplasia of lymphoid tissues and before the peak of monocytosis in the blood has been reached, all stages of transition between lymphocytes and monocytes can be seen in the lymphatic tissues of the spleen and mesenteric lymph nodes. These findings indicate, therefore, the existence in the lymphatic tissues of an important reserve of mesenchymal cells from which macrophages may be derived. The importance of the latter is indicated by the experiments of Robertson and coworkers (37, 38, 39). They have shown that, in experimental canine lobar pneumonia, local disposal of pneumococci and local recovery are due almost entirely to the local macrophage reaction

in which the fixed tissue phagocytes of the lungs acquire an increased reactivity. Ross (40), in a study directed to the problem of the origin of these cells, has concluded that they arise in the connective tissues of the lungs and migrate across the alveolar septa into the alveolar spaces.

Effects of heredity and environment.—The influence of heredity upon resistance to infectious disease is gradually becoming more apparent. Webster & Hodes (41), in an extension of earlier experiments of the former, have shown that, after exposure of groups of mice to natural mouse typhoid infection, the mice from strains of innately high susceptibility have a high fatality rate whereas those of innately high resistance survive, although the infection rate, as shown by spleen cultures, is approximately the same in both groups. These findings indicate, therefore, that degrees of infectivity and lethality depend upon factors residing in the host rather than in the bacteria. The predominant role of inborn resistance was indicated, also, by the fact that at no time did the known susceptibles become immunized through herd exposure. Church (42) has shown, in corroboration of the findings of Webster & Hodes, that resistance to the intragastric inoculation of *Salmonella enteritidis* is definitely enhanced in selectively bred strains of resistant mice. His studies, utilizing approximately 3000 mice, demonstrate the greater fitness of the highly resistant strains. He found also that resistance of the host is not readily affected by changes in the current diet, except that a low mineral supply led to an increased fatality rate. He showed, however, the importance of the maternal diet in that mice from mothers on a deficient diet are much more susceptible to infectious disease. Lurie (43) has subjected groups of inbred rabbits to contact infection with tuberculosis and has concluded that the genetic constitution influences largely the type and severity of the disease resulting from first contact with tuberculous animals. He has recorded observations suggesting that resistance is correlated with lesser degrees of cutaneous permeability, less intense inflammatory reaction against the tubercle bacillus and a greater speed both in the evolution and the healing of tubercles.

The effects of environmental changes upon resistance, particularly the influences of changes of body temperature, weather, fatigue, shock, etc., are being examined further. Locke and associates (44, 45, 46, 47) have shown in rabbits that "fitness" to

withstand infection may be predicted to a considerable degree by a determination of the "warming time," i.e., the time required in minutes for the recovery of three degrees of body-temperature following chilling to a point between 95°C. and 96°C. They have observed that animals with a prolonged warming time are less able to dispose of virulent pneumococci injected into the blood stream, due, presumably, to an inadequate circulation and an impairment of ability to maintain body temperature and tone. They have found, furthermore, that concurrent snuffles and related low grade infections have a similar depressing effect on the ability to withstand pneumococcic infection. On the other hand, spontaneous or artificially induced shortening of the warming time after chilling definitely increased the resistance of rabbits against pneumococcic infection. Locke has also suggested that fatigue may, through its effects upon oxygen consumption, affect tissues adversely and at times predispose to respiratory infections, particularly the common cold. Petersen (48), in a series of monographs, has advanced the view that variations in autonomic reactions leading to changes in vascular permeability are induced by meteorologic changes, and that because of the resulting anoxemia of tissues, adventitious microorganisms may establish infections. The importance of fatigue and shock as factors tending to favor the development of leukopenia are emphasized also by Reznikoff (49) and van Duyn (50). The influence of temperature upon infectious processes has been studied by Thompson (51), Dyson (52) and Doan (53). Thompson, who injected the viruses of infectious fibroma and infectious myxoma into rabbits and observed that when the temperature of the skin was increased the development of the lesions of fibroma virus was inhibited, suggested that this virus is able to parasitize the skin because of its lower temperature but cannot develop within the body because of the higher temperature. Furthermore, animals infected with myxoma virus and kept at a temperature of from 36°C. to 40°C. exhibited an enhanced resistance, suggesting that the poorer development of the virus in the skin may have been due to the higher temperature. Dyson observed that hemolytic streptococci isolated from a patient with acute rheumatic fever grew much less readily in defibrinated blood at 40°C. than at 37°C. and suggested that the higher temperature of fever in the body might similarly interfere with streptococcic growth in the tissues. Doan studied the blood response in patients

in whom fever had been induced either by the Kettering hypertherm or by injection of typhoid vaccine or malaria parasites and concluded that such high temperatures induce a post-febrile leukocytosis and an increase in macrophages in the lymph nodes, spleen and liver. The effect of the higher temperature, therefore, is a stimulation of mesenchymal tissues. Exposure to cold may also depress resistance and Nungester (54) has demonstrated that rats may be made more susceptible to pneumonia by chilling, due to a resulting interference with closure of the glottis and a greater tendency to aspirate infectious material from the upper respirator passages.

Vitamin deficiencies.—Deficiency in vitamins, particularly A and C, affects natural resistance, although just how is not certain. The effects of deficiency in vitamin A have been discussed recently by Bessey & Wolbach (55) and by Clausen (56). Deficiency in this vitamin when pronounced, leads to atrophic changes in epithelia and the development of a keratinizing metaplasia. The keratinized epithelial cells may, in glands and ducts, cause occlusion, followed by secondary infection with adventitious bacteria. In the lungs of lower animals and of human infants these plugs of desquamated epithelial cells may predispose to bronchitis and alveolitis. Chown (57) has recently reported five cases of giant cell pneumonia in children and has discussed the possibility that they may be due to a deficiency in vitamin A. In general, however, according to the evidence now available, vitamin A deficiency is not usually of a severe enough grade in the human being to produce marked changes but it may assume more importance under war-time conditions of prolonged malnutrition. Evidence accumulates that vitamin C plays an important part in resistance. This vitamin is concerned with the formation of collagen and the deposition of intercellular cement substance but may influence immune mechanisms in other ways as well. For example, there is evidence that it is related to complement of the blood (58, 59). Giroud (60) has reported a marked difference in mortality from spontaneous infection in rabbits on a low vitamin C diet as compared with those on a high vitamin C diet, but unfortunately, gave no figures as to the numbers of animals observed. Philippe & Baratte (61) have shown that guinea pigs deficient in vitamin C do not form antitoxin against diphtheric toxoid as well as normal animals or as do those given excessive amounts of vitamin C in their diet. Cameron (62) reports similar

results after the use of ascorbic acid, but calls attention to the possibility that the depressed formation of antibody may be due to inanition accompanying the vitamin deficiency. Rinehart and his associates (63) report a low content of cevitamic acid in the blood plasma of patients with acute rheumatic fever and conclude that this, coupled with the history of vitamin C inadequacy in the diets of so many patients with acute rheumatic fever, strengthens the concept that vitamin C deficiency may be of etiologic significance in this disease. McCullough (64) has demonstrated a definite depression in resistance of guinea pigs with severe scurvy, when infected subcutaneously with *Bact. necrophorum*. There are several statements in the literature that vitamin C protects against drug idiosyncrasies and anaphylaxis, and Rosenberg (65) has reported a deficiency in vitamin C in the blood of patients with urticaria who showed clinical improvement under treatment with citrus fruits. Eyer, Dragstedt & Ramirez de Arellano (66) and Raffel & Madison (67), however, found that vitamin C has no effect upon sensitization or protection against anaphylactic shock in dogs or guinea pigs sensitized against a foreign protein. It has also been claimed that vitamin C therapy is beneficial in whooping cough, but Gairdner (68) reports no striking effect when large doses were given and concludes that there is no proof at present that vitamin C has an effect on the course of this disease. Taffel & Harvey (69) have demonstrated, in vitamin C deficiency of guinea pigs, an impaired healing and a reduction in tensile strength of the experimental wounds. They suggest, therefore, that vitamin C deficiency in man may have a causative relation to those cases of wound disruption where there is no evidence of infection of the wound and where the patients have been on an inadequate dietary regime.

Hormones.—The suggestion that hormonal stimulation may cause the development of a so-called "maturation immunity" has aroused considerable interest in recent years. Kramer, Grossman & Parker (70) report that rhesus monkeys become more resistant to intranasal infection with poliomyelitic virus after treatment with pituitrin-S and adrephine. Sprunt, McDearman & Raper (71) have observed an enhanced resistance to vaccinia virus in castrated rabbits injected before infection with estrogenic hormone. They have found, also, that injection of this hormone promotes the more rapid localization of intradermally injected India ink. Eickhoff *et al.* (72) have reported an inhibition in the development of the

Arthus phenomenon in rabbits sensitized against a foreign protein after thyroidectomy and that, conversely, if protein-sensitized rabbits are injected with a thyrotropic hormone, they become more reactive in anaphylactic shock. Both Culbertson (73) and Perla (74) have demonstrated that hypophysectomy in adult white rats increases their susceptibility to infection with *Trypanosoma lewisi*. Culbertson found but slight effect upon resistance from the injection of anterior pituitary extract whereas Perla, using alkaline extracts of the anterior lobe, observed restoration of resistance to its normal level. Perla believes that this extract stimulates the spleen and thus acts indirectly to sustain an effective resistance. Hormonal factors, presumably, may affect acquired resistance, although in what way is as yet unknown. Hodes (75) has found that pregnancy inhibits the development of immunity and lowers the immunity already established in Swiss mice vaccinated against St. Louis encephalitis virus and infected later intranasally with the virus.

Chemotherapy.—The problem of chemotherapy is of engrossing interest at present, due almost entirely to the widespread use of sulfanilamide and related compounds. It is not surprising, in view of the rapid march of events since the advent of sulfanilamide therapy, that so many ideas should have arisen to explain the ways in which these compounds exert their therapeutic effects. Although the exact mode of action is still unknown, most of the investigators have concluded that the principal effect is bacteriostatic or bactericidal (76 to 106 incl.), modified by other factors. Many workers, for example, report that the therapeutic action may depend also upon more effective phagocytosis, neutralization of toxins or endotoxins, or interference with the formation of bacterial capsules. Several workers have suggested that the drug modifies the metabolic activities of certain kinds of invasive bacteria and thus interferes with their proper utilization of the protein substrate (79, 80, 81, 82). Bacteriostasis, according to this view, results largely from inanition because of the inactivation by the sulfanilamide of bacterial enzymes essential for the proper utilization of food. Others have postulated a metabolic disturbance which inhibits the formation of capsules and thus "disarms" highly invasive microorganisms. Levaditi (83) suggests the formation from sulfanilamide by the tissues of an x-principle which interferes with bacterial metabolism and inhibits the formation of capsules

and the production of toxins and endotoxins. Locke, Main, Mellon & Shinn (84, 85, 86, 87) assume that derivatives of sulfanilamide exert an anticatalytic action which allows hydrogen peroxide, as it is liberated by bacterial growth, to accumulate and exert a bacteriostatic effect. They point out that catalases are inactivated by hydroxylamine and related compounds and that substances similar to hydroxylamine are produced when dilute solutions of sulfanilamide are exposed to ultraviolet light. Shaffer (88) believes that the bactericidal and bacteriostatic effects may be due to oxidation products formed from atmospheric oxygen by the catalytic activity of bacteria or living tissues and points out that the bacteriostatic activity of these compounds is manifested only in the presence of oxygen. Evidence for the existence in the blood of an active oxidizing agent is shown by the frequent presence of methemoglobin in the blood of patients receiving sulfanilamide. He and others (89) have observed that sulfanilamide in broth raises the electric potential as the drug is oxidized and that the oxidation products are highly reactive and give high potentials as measured by platinum and gold electrodes. He suggests that these products, if they are not quickly reduced, are probably highly bactericidal. Locke & Mellon question certain phases of this theory and give reasons for the belief that the oxidative products are produced stepwise, the hydroxylamine derivative appearing first in the locus of infection, followed by the other derivatives in sequence.

The influence of sulfanilamide upon phagocytic activity is still uncertain. Levaditi (83) suggested that the drug tends to convert highly pathogenic bacteria into virtual saprophytes after which the phagocytes engulf and destroy the devitalized microorganisms. Finkelstein & Birkeland (107) have reported a definite enhancement of phagocytosis when varying dilutions of sulfanilamide were mixed with hemolytic streptococci, washed leukocytes and fresh serum. Gay & Clark (108) concluded that bacteriostasis acts indirectly to favor phagocytosis in that it allows time for the local accumulation of macrophages and the subsequent ingestion of the chemically injured microorganisms. There is no evidence that sulfanilamide itself attracts leukocytes, in view of the experiments of Coman (109) demonstrating the lack of any chemotropic action of the drug. Tunnicliff (110), as a result of tests made both *in vivo* and *in vitro*, maintains that sulfanilamide does not act as a sort of

chemical opsonin, but stimulates leukocytes directly to increased phagocytic activity. Opposed to this is the view that capsular degeneration or interference with the formation of bacterial capsules promotes, indirectly, a more vigorous phagocytosis (83, 111, 112, 113). Osgood & Brownlee (114) found that phagocytosis was enhanced when sulfanilamide was added to a mixture of human bone marrow and hemolytic streptococci, but assumed that the effect was indirect and consequent to the neutralization of bacterial toxins. Mellon, Gross & Cooper (115) and Long, Bliss & Feinstone (116), on the other hand, have found no conclusive evidence pointing to the importance of phagocytosis in association with sulfanilamide action. It is of interest, however, that recent papers indicate that sulfanilamide and sulfapyridine are more effective therapeutically in conjunction with immune serum than if either drug or serum are given alone, suggesting that phagocytosis may play a part in the final disposal of the infective agents (117, 118).

The suggestion that sulfanilamide acts to neutralize bacterial toxins and to combine with endotoxins (83, 119) has not been substantiated by many of the later investigators. Osgood & Powell (120), for example, found that sulfanilamide *in vitro* had no significant neutralizing action against hemotoxins of several different species of bacteria, nor against the toxic action in guinea pigs of diphtheria or tetanus toxins. Long, Bliss & Feinstone (116) observed that "high concentrations of sulfanilamide in the blood do not alter positive reactions to the Dick test in human beings," and Lockwood and associates (80) found that sulfanilamide had no effect on the toxemia of scarlet fever. Hemmens & Dack (121) observed that, in rabbits infected subcutaneously with *Bact. necrophorum*, sulfanilamide acted to restrict the spread of the lesion and the growth of bacteria in it; inasmuch as this bacterium does not produce a toxin, the action was obviously not antitoxic. Other workers have come to similar conclusions (122, 123, 124, 125), although Carpenter & Barbour (126, 127) more recently have reported observations indicating a neutralizing action of sulfanilamide and neoprontosil toward several bacterial toxins, although the effect *in vivo* was less marked than *in vitro*.

Specific Mechanisms of Defense

The problem of the nature and functional significance of specific antibodies has long occupied the attention of immunolo-

gists. It is now apparent that the ordinary antibodies are specifically modified globulins. Sabin (128), by the use of a dye-protein which when injected into the body served as a "tracer," observed that, after phagocytosis of the dye particles, antibodies appeared in the serum at the time when the dye-protein was no longer visible within the cells and as the latter were shedding surface films. She assumes, therefore, that the antigen specifically modifies the synthesis of globulin so that the shedding of parts of the surface films actually liberates normal globulin and antibody globulin into the blood and tissue fluids. She suggests, furthermore, that such a cell, because of its synthesis of a new kind of globulin within its cytoplasm, may thus be "sensitized," i.e., have acquired an altered reactivity upon later contact with the specific antigen. This changed reaction-capacity of tissues induced by infection or artificial immunization constitutes one of the perplexing aspects of immunity. Because of the fact that the part played by antibodies is so uncertain, some have postulated the existence of a tissue-immunity largely and perhaps entirely separate from serological immunity. Francis & Stuart-Harris (129, 130, 131) have studied the histological changes in the epithelium of the upper respiratory tract of ferrets after intranasal instillation of influenza virus and have shown that during repair the epithelium becomes an undifferentiated low transitional type tending toward a stratified squamous variety. If, during this stage, influenza virus is reintroduced into the nose, no infection occurs, but increased susceptibility returns when the epithelium once more reverts to the highly differentiated ciliated type. Even then, however, the epithelium is more reactive than normal to the introduction of influenza virus and the reparative process proceeds more rapidly. Resistance seems to be related both to antibody titer and to the non-specific reparative capacity of epithelium. Hodes & Webster (132) have shown that the susceptibility of cerebral tissues of mice infected with St. Louis encephalitis virus is not influenced greatly by the presence of neutralizing antibodies in the blood of vaccinated mice. Gordon, Hudson & Harrison (133) have observed a similar lack of correlation between the presence of antiviral substances in the blood and the ability of monkeys to resist intranasal infection with the virus of poliomyelitis.

Active immunization.—Efforts continue in the attempt to develop better types of vaccines for the attainment of specifically increased resistance. Bedson (134) has found that a considerable

immunity to the virus of psittacosis in mice can be secured by previous injection with a formolized vaccine. Kligler & Bernkopf (135) have demonstrated, similarly, that mice may be protected against rabies by intraperitoneal immunization with a formolized tissue culture of rabies virus. Beard, Beard & Finkelstein (136) have recently prepared a formolized vaccine from the virus of equine encephalomyelitis grown in chick embryo and have induced the development of neutralizing antibodies in human beings. Improvement in the mode of vaccination against smallpox has been attempted by Rivers and his associates (137) by the cultivation of a vaccinia virus in a medium of chick embryo tissue and Tyrode's solution. Under these artificial conditions this virus has become changed qualitatively so that considerable amounts can be injected intradermally into human beings without danger. The authors point out, however, that the degree of immunity engendered is probably not sufficient for complete protection against smallpox and they advise therefore that individuals vaccinated with the culture virus should be vaccinated dermally from six months to a year later with potent calf lymph virus, in order to secure a lasting immunity against smallpox. They advocate this measure at least until a cultured virus can be developed whose immunizing potency can be maintained continuously in artificial media. Mention should also be made of the encouraging results in the development of a vaccine against Rocky Mountain spotted fever, made from infected ticks (138).

Newer developments in the preparation of bacterial vaccines should be noted. Freund & Opie (139) have demonstrated that rabbits can be immunized against tuberculosis by vaccination with heat-killed tubercle bacilli, encouraging the hope of vaccinating human beings with other than living microorganisms. Felton and his coworkers (140, 141) have presented evidence suggesting the possibility of immunization against pneumonia by means of an antigenic polysaccharide obtained from pneumococci. This material is water-soluble, is stable and therefore easily sterilized, confers immunity in white mice against certain types of pneumococci and engenders antibodies in human beings. Progress is also being made in the demonstration of a favorable influence of vaccination against whooping cough with a vaccine of *H. pertussis* (142, 143, 144).

Passive immunization.—Although the intense interest in

chemotherapy has tended to divert attention from serotherapy, progress continues in the latter field. Particularly noteworthy is the development of type-specific antipneumococcic rabbit serum. Horsfall (145) has enumerated the principal differences between antipneumococcic rabbit and horse serum including certain therapeutic advantages of the former, particularly the absence of prozone action, the probably greater permeation of tissues because of its smaller antibody globulin molecules, its greater effectiveness in mouse-protection in pneumococcic infection, and its lesser tendency to cause serum-disease. Heidelberger and associates (146) have prepared an antibody globulin from this serum which, when diluted with saline, gave practically no reaction in patients. Horsfall, Goodner & Macleod (147) and Loughlin, Bennett & Spitz (148) have reported favorable results from the use of the rabbit antipneumococcic serum in the treatment of lobar pneumonia. The mortality rates in their patients, exclusive of type III, varied from 3 per cent to 7 per cent. Leslie & De Sanctis (149) and Appelbaum (150) report evidence favoring the intraspinal use of antiserum in meningococcal meningitis, but emphasize the importance of employing potent serums. These writers use the serum intravenously only in conditions of persistent bacteremia. Sheplar, Spence & MacNeal (151) report favorable and encouraging results in the treatment of streptococcic infection with the use of a concentrated antistreptococcal serum prepared by the New York State Department of Health.

The use of convalescent serum in the prevention and treatment of childhood diseases (measles, mumps, whooping cough, chickenpox and scarlet fever) is becoming more widespread as more serum centers are being established. Hyland and associates (152) have recently discussed many of the aspects of this problem. Because of the restricted usefulness of convalescent therapy due to limitations in supply, McKhann (153) advocates the use also of immune globulins extracted from human placentas and has reported good therapeutic results with this material. Felsen & Osofsky (154) have shown that mice may be protected against infection with a moderately virulent strain of *Shigella dysenteriae* by injection of serum from immunized rabbits.

Functional role of specific precipitins and agglutinins.—The importance of specific precipitins in resistance is indicated by experiments of Taliaferro & Sarles (155, 156). These workers have

demonstrated in the white rat the inhibiting effect of these antibodies upon the growth and migration of larvae of *Nippostrongylus muris* and have described the formation, in immune rats, of a precipitate in the mouth and digestive tract of the larvae, accompanied by intensified inflammation, restriction of growth and limitation of migration of the parasites. This precipitative reaction was demonstrated both *in vitro* and *in vivo*. Kerr (157) has observed a similar type of enhanced resistance in guinea pigs immunized against pig ascaris. Later infection was characterized by a delayed growth and a more rapid destruction of the larvae in the livers of the resistant animals. The role of precipitins in the process was not established. Gins, Kroemer & Link (158) and Hammerschmidt (159) have demonstrated the superior ability of immune tissues to localize bacterial infection. The former workers emphasized the importance of bacterial agglutination antecedent to the accelerated inflammatory reaction as a phenomenon contributing to the speedier disposal of the infectious agents. Hammerschmidt also demonstrated the more effective localizing potentiality of immune tissues for infectious agents, although he attributed the effect to the presence of antiaggressins rather than to agglutinins. Eaton (160) has detected the presence of agglutinins in the serums of monkeys infected with *Plasmodium knowlesi* for as long as a year or more after infection and has suggested their possible relationship to the enhanced phagocytosis and resistance observed in superinfection. Evidence of a functional role of agglutinins is furnished, also, by the demonstration by Frisch (161) of agglutinated clumps of pneumococci in the sputum of patients with lobar pneumonia after treatment with specific antiserum. Associated with the agglutinative phenomenon was a more effective phagocytosis. Schmidt (162) has reemphasized the necessity of taking into account the role of precipitins in the blood of patients hypersensitive to horse serum, when injected with antitoxic serums. He showed, in rabbits sensitized against horse serum and injected intravenously with antitoxic horse serum, a direct relationship between the precipitative potency of the serums and the speed with which the antitoxin was removed from the circulation. He pointed out that under similar conditions in the human being, the antitoxin is probably removed from the blood too quickly to be utilized adequately.

The problem of local formation of antibodies and of local or

regional tissue-immunity has been explored further. Orskov & Andersen (163) have demonstrated the presence of antiviral neutralizing substances, presumably formed locally, in the skin of rabbits infected intracutaneously with vaccinia virus. Dick & Dick (164) have shown that a local immunity to the toxin of the streptococcus of scarlet fever may be produced, by intradermal injections of the toxin, in the skin of human beings. They suggest that when repeated tests for susceptibility to scarlet fever are to be made, they should be made in areas of skin not previously injected, in order to avoid false results from the injection into areas of partial local antitoxic immunity. Walsh & Cannon (165) found in rabbits immunized by different routes, a greater concentration of specific antibody in regionally immunized tissues than elsewhere and suggested that this fact may offer a means of enhancing local mechanisms of defense, either by the local formation or the local accumulation and retention of immune bodies in areas likely to become infected.

Functional aspects of allergic reactions.—The varied problems of allergy continue to occupy the attention of many workers, and several significant papers have appeared which throw light on the mechanisms involved. Abell & Schenck (166), utilizing the method of the insertion of transparent chambers in the rabbit's ear, have recorded the development of vascular reactions in anaphylactic shock. They observed, both in shock after the intravenous injection of the antigen as well as after its introduction into the chamber, progressive vascular changes including arteriolar contraction, obliteration of lumina, and blood stasis, accompanied by increasing adherence of leukocytes to endothelium and diapedesis into the surrounding tissues. The leukocytes also stuck to one another in many capillaries and venules and formed emboli which blocked the circulation. Whether the reaction is secondary to nerve stimulation or to a direct union of antigen and antibody within the blood vascular wall was not determined, although it is reasonably certain that it was produced locally rather than indirectly. Hehre & Freund (167) have clarified some of the uncertainty about the significance of cutaneous allergic inflammation by showing that rats infected either with highly virulent bovine tubercle bacilli or vaccinated with heat-killed tubercle bacilli may be highly allergic to tuberculin when it is injected intra-abdominally and yet may fail to react when it is injected into the skin, indicat-

ing that species differences in cutaneous reactivity exist and that failure to recognize this may lead to erroneous conclusions as to the relationship of allergic inflammation to resistance.

The mechanism of atopy (hypersensitiveness in human beings with no history of sensitization and with a strong hereditary predisposition) is still one of the puzzling problems of allergy. Several groups of workers, however, have recently thrown more light on the subject. Walzer and his associates (168) have sensitized rhesus monkeys passively by the injection into the wall of the gastrointestinal tract and elsewhere of atopic serums from patients hypersensitive to cottonseed oil. When such animals were later injected intravenously with the specific antigen, blanching, hyperperistalsis, hyperemia, edema and increased secretion occurred. These studies are interesting also because of their similarity in many respects to those of Abell & Schenck in anaphylaxis. Sherman, Stull & Hampton (169) have induced passive sensitization of human skin by the injection into it of serums from animals sensitized to pollen extracts. Although the results were not uniform and the reactions were not as intense as those usually obtained with human serums, they were nevertheless specific and the reagins were absorbable by homologous antigen. Sherman, Kaplan & Walzer (170) also passively sensitized the nasal mucous membranes of the inferior turbinate and septum of 26 of 31 human subjects by the injection of reagin-bearing serum (ragweed pollen). The local hypersensitiveness lasted for weeks and could be exhausted by repeated tests with the specific antigen. These types of experiment are interesting particularly because of their similarity to the well-known reactions of anaphylaxis in animals. Of great interest, also, are the experiments of Eagle, Arbesman & Winkenwerder (171, 172) demonstrating that specific antibodies (precipitins, sensitizing and complement-fixing) can be readily engendered in rabbits by the injection of extracts of pollens and that characteristic anaphylactic shock can be produced in guinea pigs by passive transfer of these serums as well as by active sensitization with the pollens. Furthermore, sensitization of normal human skin was accomplished in about half of the experiments by the injection of serums from guinea pigs sensitized against pollen extracts. These findings strengthen the views of those who maintain that the allergic or atopic reactions are fundamentally identical in nature

with anaphylactic phenomena, even though complete proof is as yet lacking.

Sensitization to drugs and chemicals constitutes also an increasingly important medical problem and the mechanisms responsible are still not well understood. Experimental sensitization to known chemical substances has been produced by Sulzberger & Rostenberg (173) by direct application to the skin of human beings of p-nitrosodimethylanilin and 2,4-dinitrochlorbenzene. They observed that individuals with recent or active contact-types of eczematous dermatitis became sensitized in about half of the cases and concluded that such persons are more likely than are normal individuals, to acquire sensitization to additional eczematogenous allergens. Golden & Gierson (174) have sensitized guinea pigs against amidopyrine by the daily injection for twenty-five days of small amounts of this drug. These findings are of interest in view of the suggestion that agranulocytosis associated with the ingestion of amidopyrine may be due to an idiosyncrasy to the drug. Landsteiner & Di Somma (175) have induced sensitization to diazomethane in guinea pigs and to mustard oil in man and in swine by repeated local applications to the skin. Landsteiner & van der Scheer (176) have shown also that azo dyes are precipitated directly when added to antisera against azoproteins and cause anaphylactic shock when injected into sensitized guinea pigs, indicating that the azo dye may react directly and does not need to combine with a protein in order to react.

The papers cited comprise but a portion of those published during the period reviewed (1938 and a part of 1939). An attempt has been made to present only those which relate predominantly to physiological processes in a field not usually surveyed by physiologists. More detailed discussions are available in the following reviews: the immunology of helminthic infections [Culbertson (177)]; the role of vitamins B and C in resistance [Perla (178, 179)]; the problem of allergic inflammation and its effects [Stenn (180), Smyth (181)]; the significance of the "complex infections" [Shope (182)]; the relationship of nutrition to resistance [Robertson & Tisdall (183)]; the chemotherapy of bacterial infection [Garrod (184)]; the pathology and mechanism of anaphylaxis and its relationship to shock [Moon (185)]; and the influence of age upon resistance [McKhann & Kapnick (186)].

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EXERCISE

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The physiologist has an abstract interest in the mechanism of a variety of phenomena which differentiate the quiescent from the active organism and, like the clinician, often utilizes exercise as a test strain through the application of which the functional capacities of the machine may be evaluated. On the other hand, those practically interested in the physiology of man at work, industrial or recreative, largely limit their attention to methods of testing and improving performance. In drawing the minutiae contributed by workers possessing such divergent views into a resumé of recent progress, a certain degree of relationship may be developed between them if exercise is looked upon as a means to practical rather than theoretical objectives.

Interrelations between Exercise and Body Type and Their Relation to Reproductive Functions

Škerlj (1) made an extensive anthropometric study of picked Polish athletes and concluded that intensive sport participation affects the female more than the male, favoring the development of infantile and viril body types and a high incidence of menstrual irregularity. He (2) classifies the bodily configuration of Central European women into eight feminine types. Adams, however, obtained no evidence that hard labor during youth tends toward the development of a significant degree of maleness in the build of young American colored women. Carpenter (1) found that when it occurs, masculinity of build has a favorable influence upon athletic ability but that muscular strength and power are of much greater importance. Pryor & Smith observed that the broad, lateral type of adolescent girl consistently possessed a physical capacity superior to that of the linear type of girl. Carpenter (2) presents a resumé of the practical strength testing literature.

Strugurescu reports transitory modifications of the menstrual function among athletic women, which disappear with the cessation of heavy exercise programs. Muscular work had a favorable influence upon some, and it is concluded that there should be no

prohibition of physical activity during the menses. Exercise had no detrimental effect upon fertility, and the supposed increase in the strength of the pelvic floor musculature resulting from participation in competitive athletics appears to have no pathological influence upon labor [Knoll (1); Franz].

Recruits in the Bucharest garrison and contestants in the 1937 Balkan Olympics have been subjected to large scale anthropometric studies related to physical performance (Mihăiiă & Ulmeanu; Ulmeanu; Ulmeanu & Mihăilă). Milco & Walter found the flattest longitudinal arches in long distance runners. Sprinters had smaller feet and higher arches. The importance Basler (1) attributes to the function of the toes in standing is not borne out by the more precise methods of Kelso & Hellebrandt and Hellebrandt *et al.* (1, 2) who project the center of gravity into the base of support.

Posture

Neck and labyrinthine reflexes and the righting reflexes are normally suppressed by the cortex. Bieber & Fulton found that they did not reappear in monkeys and baboons until both motor and premotor areas had been ablated. Evans & Ingram consider tonus inhibition an extrapyramidal function, while placing and postural adjustment reflexes are thought to be of pyramidal origin. Gesell finds the tonic neck reflexes a virtually universal feature of normal infancy up to the age of three months. Byers interprets their presence in older infants and adults as a retention or reappearance of a primitive response released by absence or loss of functionally more mature postural mechanisms. Weisz studied the appearance and loss of the body righting reflexes in human infants and children and believes it is difficult to say if they disappear, or are suppressed, in the course of development. Dow has studied the action potentials of the anterior lobe of the cerebellum and finds postural tone inversely proportional to the electrical activity of this portion of the brain. Harris reports that cutaneous fibers in the medial plantar nerve are capable of eliciting an ipsilateral extensor reflex of the slow postural type which is difficult to fatigue and has its focus in the ankle extensors, in contrast to Sherrington's extensor thrust which involves mostly the hip and knee. Hellebrandt *et al.* (3, 4) locate the center of gravity in the cardinal anatomical orientation planes and discuss standing as a geotropic reflex. Tepper postulates a relation between the energy cost of

standing and the type of contraction necessary for the preservation of the stance.

Asmussen, Christensen & Nielsen present an important series of papers on the influence of posture on the regulation of the circulation. There is a practically linear augmentation of heart rate with increasing hydrostatic handicap which may be eliminated by diverting the flow away from the legs. Asmussen and his associates interpret this to mean that normally even small changes in blood distribution are not adequately compensated for by corresponding changes in the blood depots. Krogh, summarizing their work, agrees that there is no complete adaptation to passive standing in man. McDowall's monograph contains a comprehensive review on the circulatory adjustments to the vertical posture.

Keys & Butt have studied the filtration processes in the extremities on standing. On the basis of tissue pressure observations, Wells, Youmans & Miller conclude that leg volume continues to increase indefinitely in the low pressure filtering areas during quiet standing. Weiner states that South African Bantu were able to shovel gravel for one hour at 94 to 95 degrees F. and then stand at attention for another hour or longer, a finding totally incompatible with the "gravity shock" concepts of Mateeff and Mateeff & Petroff. Postural sway is inseparable from the upright stance and unless prevented by firm restraint is of very material value to the maintenance of an adequately effective circulation [Hellebrandt *et al.* (5, 6)]. Postural contraction seems to be composed of numerous quick movements associated with sharp changes in intramuscular pressure, too small to be detectable by ordinary means and hence giving the appearance of smooth and steady holding [Hellebrandt *et al.* (7)]. Mayerson & Burch find that low intramuscular tissue pressure is a significant underlying factor in the occurrence of postural syncope.

Electrocardiographic changes difficult to interpret have been reported by Sigler and by Perschmann with alterations of posture. Hitchcock & Ferguson observed only very moderate effects of standing upon respiratory activity contrary to Brogdon & Hellebrandt who found that orthostatic hyperpnea might be extreme to the point of Cheyne-Stokes breathing when the muscle pump was thrown out of action. Main & Baker find that there is no increase in the velocity of the circulation in the upper part of the body to help keep up the cardiac output in the face of a reduced circulating

blood volume. Mayerson, Sweeney & Toth show a decrease in the velocity of the blood flow in the lower extremities, attributable to pooling in the veins.

Movement

The biodynamics of human locomotion, terrestrial and aquatic, have been studied respectively by Elftman and Karpovich & Pestrecov. Hubbard & Stetson conclude from simultaneous action current, deformation, and movement studies that the agonist develops tension for its driving contraction chiefly during the stroke in the opposite direction which precedes the one it causes. They assume that the rectus femoris causes the forward stroke of the freely swinging leg. Their paradoxical finding suggests that the flexion is being caused by a different muscle than the one studied, i.e., the ilio-psoas. The action current in the rectus femoris during the back swing may be due either to stretch or to contraction in an effort to keep the knee joint extended. An interesting departure in the study of muscle action is Stewart's cinematographic analysis of gait variations following partial destruction of the tendon of insertion of one or more groups acting on a joint.

Motor Learning

Langworthy & Richter demonstrated the protective inhibitory control exerted by the cortex over the lower motor neuron by their observations of increased spontaneous activity in cats after removal of the frontal poles of the brain. So great was the release that some of the animals died directly or indirectly from exhaustion. From a study of rhythmic cortical potentials in their relation to involuntary tremors, Jasper & Andrews propose that the cortex may inhibit the subcortical discharges or take over the dominant control of the final common path during voluntary contraction. Mettler *et al.* stimulated the nuclei of the extrapyramidal system during movements experimentally produced from the cortex and so succeeded in demonstrating the impartation of plastic tonus and other conditioning manifestations upon movements originating elsewhere. From a study of after-contraction, Sapirstein, Herman & Wechsler reason that with a large initial stimulus, the after-discharge from the cortex or its projection pathways should lessen the voluntary effort required to initiate the discharge needed to achieve the end desired and that this phenomenon may play

some role in the training of motor habits. A baseball player warms up by swinging two or three heavy bats before going to the plate. Using multiple co-axial needle electrodes, Hoefer & Putnam observed that individual motor units appear to alternate without obvious regularity as mild voluntary contraction is sustained, adding weight to the surmise that phasic contraction and tonus differ only in the synchronicity of their motor unit response. However, Speidel (1) could discern no histological differences between resting fibers and those in a state of neurogenic tonus.

The issue between the "total pattern" and the "reflex theory" of motor learning has been discussed by Barcroft & Barron and by Kuo, who feels that neither school has secured sufficient convincing evidence. So far as the sheep is concerned, Barcroft observes that local motor mechanisms seem to segregate out of total responses in Coghill's sense. Practical studies of motor learning with implications of physiological interest have been made. Wild analyzed the growth, between the ages of two and twelve years, of a specific motor pattern, and Keeler studied the effect of maturation on skill at a higher age level. Irwin found that a higher percentage of children were ambidextrous with respect to the feet than the hands but that many, performing physical activities right-handedly through eduction, were inherently ambidextrous.

Contraction, Fatigue and the Fuel for Muscular Exercise

Lundsgaard reviews the contributions of his laboratory, and Simonson presents a general discussion of the energy exchanges during work. Contracting muscle may be capable of direct utilization of energy arising from oxidative processes. Substances other than those liberated during anaerobic contraction appear to be involved in the supply of energy. Flock, Ingle & Bollman have verified that in mammalian muscle with an intact blood supply the rapidly accumulating compounds associated with anaerobic processes seem to be little involved in the maintenance of continuous work. The muscles at first contract anaerobically but all formation of lactic acid soon ceases. Its concentration falls, even as work proceeds. This substantiates Sacks, who postulates a functional independence of the aerobic and anaerobic mechanisms in the catabolism of carbohydrate in the steady state. Sacks pictures the ability to derive energy for contraction from anaerobic processes as an emergency mechanism such as arises each time the organism

passes rapidly from rest to vigorous activity. Only during the lag period of circulatory adjustment, when the supply of oxygen is inadequate to support the suddenly augmented metabolism, do anaerobic reactions take place.

Christensen & Hansen present a series of brilliant papers on the combustion processes in severe and protracted work. Such exercise was associated with hypoglycemia and increased utilization of fat. The subjects could work two or three times longer on a carbohydrate-rich diet than on a fat-rich diet. In the presence of hypoglycemia and great fatigue, the capacity for work could be improved by the administration of sugar. Christensen & Hansen then postulate that the fatigue of protracted exhaustive exercise is a hypoglycemic symptom. It has a cerebral origin. This concept is well supported by the work of Glickman & Gellhorn and Gellhorn *et al.*, who have observed that a low blood sugar interferes with the oxygenation of the central nervous system to such an extent that a mild degree of oxygen want brings on symptoms similar to those obtained at normal blood sugar levels only under conditions of extreme anoxia.

Christensen & Hansen postulate that the liver may have importance for the "regulation" of the respiratory quotient. It is known that ketone bodies may be utilized as a fuel in muscular exercise. The variable capacity of the liver for ketone formation may therefore be a limiting factor in the catabolism of fat. This falls off with an arrest of ketone formation in the glycogen-rich liver. Selye finds that excessive muscular exercise is associated with acute fatty infiltration of the liver, most marked if the animals fast during work. Courtice, Douglas & Priestly showed that after moderate but prolonged exercise performed in the post-absorptive state there was a low respiratory quotient, ketonuria, and a delayed reduction in glucose tolerance, similar to that characteristic of a low carbohydrate and high fat diet. Haldi *et al.* (1) could ascertain no correlation between muscular efficiency and the respiratory quotient prevailing at the onset of exercise.

Grubbs & Hitchcock presume that the muscles are capable of using the energy of ethyl alcohol in performing work. They find that the oxidation of alcohol takes place at a higher rate sitting than prone, and still higher working than sitting at rest. Carpenter & Lee contend that the metabolism of alcohol proceeds at about the same rate irrespective of rest or work.

Ray, Johnson & Taylor estimate invariable increases in the capacity of the male to perform work as a result of the ingestion of gelatine. This they attribute to the creatinogenic action of its glycine. It is difficult to understand the enormous difference in the work performance between the male and female in their published graphs and the failure of the female to show any really significant training effect during forty days of work. No data are given concerning the duration of the effort, although work output is reported in units which cannot be used without reference to time.

Mirski and his associates exercised rats to exhaustion. The large carbohydrate reserves in the liver of animals on a carbohydrate-rich diet disappeared rapidly, in contrast to the smaller reserves of the protein-fed. Excessive catabolism of protein appears to act as a powerful incitant to glyconeogenesis. Glycogen is freshly formed even under the stress of heavy carbohydrate demands.

On indirect evidence Chrometzka & Witten declare that the traditional high protein diet of the sportsman is not physiological and Lehmann (1), discussing dietetics for the population from the point of view of bringing about the highest capacity for work, also tries to justify forced minimal values on the basis of "newer views" which purport to place previous needs too high. These efforts are not in accord with the old observations of Wishart who noted the best performance of a long distance racing cyclist on high protein diets. Kraut, Lehmann & Bramsel have developed a new schema for the purpose of dietary calculation which expresses occupational caloric needs as a percentage of the basal value, modified by age, sex, and build. Recent progress in Industrial Physiology is discussed by Lehmann (2) and by Dill (1). Part II of Atzler's review has come to press.

A review on fatigue has been written by Wajzer. Since fatigued muscle takes up water, Shafer & Skow suggested that fatigued neurons might similarly increase in size, but procured only contradictory findings. Scarborough saw no change in the Nissl granules of the nerve cell after prolonged stimulation of autonomic ganglia. Adelhelm fatigued rats until they fell exhausted. The Golgi material in the striated muscle fibers showed fragmentation but the mitochondria appeared normal.

The administration of phosphate has little influence on the work capacity of dogs running in a treadmill, according to Morse.

Hollaender assays the whole of the work on the mitogenetic radiations of Gurwitsch which supposedly weaken or disappear as a result of heavy exercise and concludes that the detection of the rays rests on a unsound basis. Hartwitch advocates the use of cardiazol as a prophylactic against athletic exhaustion which predisposes to injury, and Abrahams presents a short review of recent evidence concerning alcohol and tobacco in the training regimen of the sportsman. Macht & Macht found that cobra venom increases neuromuscular coordination and ergographic work. The effect of epinephrine in counteracting fatigue is believed by Burn to be due to improved terminal transmission of the motor impulse. Luco thinks that by lowering the threshold to acetylcholine, epinephrine permits the decreased amounts liberated during fatigue to become effective. This may explain also the Orbeli phenomenon, sympathin having effects similar to those of epinephrine. On sympathetic stimulation, fatigued muscle responds by doing more work in spite of diminished blood flow (Bülbring & Burn).

Vitamins

Weiss, Haynes & Zoll observed that B_1-deficient rats showed a marked decrease in spontaneous activity and a defect in lactic acid metabolism. Flock & Bollman, however, report that although B_1-deficient rats have a higher initial concentration of pyruvate than controls in both blood and muscles, the exercise increase does not differ. Guerrant, Dutcher & Chornock report that rats on a diet supplemented with vitamin A were more active than controls and that those forced to exercise showed sign of deficiency later than confined animals. Exercise had a depressing effect on the rate of growth irrespective of the vitamin A intake. Black & Murlin, studying the effects of protein, also observed that exercised rats grew less than sedentary ones. However, Haldi *et al.* (2) found that the percentage gain in weight of animals exercising at will was greater than those confined. Diets deficient in vitamin E were found by Knowlton & Hines to bring about alterations in contractile ability before outward signs of muscular weakness were evident, and in the absence of characteristic histological change. Evans, Emerson & Telford and Telford *et al.* showed that rations low in vitamin E eventually led to disability in locomotion and to the development of marked progressive degenerative changes in the muscles.

Circulatory Adjustments to Work

Tătăranu studied the morphological changes in the blood after the Balkan Marathon in Bucharest. He failed to confirm the presence of any significant increase in young leukocytic forms referred to as the "shift to the left." Kushner found that the acute rise in red blood cells and hemoglobin produced by exercise in the best stallions was considerably higher than that shown by inferior horses. Training for two months increased the number of red cells, the reserve alkalinity of the blood, and the diameter of the red cells. Davis advances the belief that the chronic increase in fragility of the erythrocytes in dogs trained to treadmill running is due to the associated rise in body temperature. Decreased red cell resistance is observed after a hot bath but not as a result of swimming. Schlutz & Morse report a rise in serum protein, chloride, and total fixed base with strenuous, protracted treadmill exercise in dogs, but a decrease with swimming, results which they attribute to differences in the transfer of fluid containing diffusible ions from the blood system to the interstitial tissue spaces. The fall in serum bicarbonate in both short violent exercise and long hard work on the treadmill is greater than can be accounted for by dehydration, overventilation, and the entrance of lactate into the blood stream.

Brouha, Nowak & Dill observed that chronically totally sympathectomized dogs possessed eighty to ninety per cent of their normal cardio-accelerator response to exercise. This was strikingly reduced by vagotomy. A part of the increase must, therefore, have been due to vagal accelerators. The cat's vagus has similar fibers. However, Hodes found that, unlike the dog, the capacity of the sympathectomized cat to endure forced work was reduced.

Herzum (1) presents a new pulse recovery test composed of two bouts of work, the second preceded by a period of hyperventilation. Dill (2) observed that exercise cannot cause extremely rapid heart rates after middle age. Training does not augment the speed with which the heart accelerates at the onset of exercise, but its retardation is distinctly bettered. McCurdy & Larson applied to over one thousand subjects ranging in age from eighteen to eighty years an organic efficiency test composed of six cardiovascular-respiratory test items arrived at by statistical methods from an original battery of twenty-six. Their group included 154 lawn bowlers between the ages of fifty to eighty years. Poorer scores

were obtained in the upper age ranges, and there was some evidence of a progressive difference in pulse rate recovery after exercise.

McDowall's recent monograph on the control of the circulation has an excellent resumé on heart size and exercise. He includes unpublished work of O'Shaughnessy, demonstrating that the cardiac hypertrophy of racing greyhounds may proceed so rapidly that the activity of the heart is impaired by lack of space. Kirch & Nürmberger subjected rats to very severe training. Hypertrophy was regularly produced, appearing as early as six days. The right side demonstrated the first and the greatest hypertrophy, which they attribute to elevated pulmonary circulatory resistance and increased venous return from the periphery. They also demonstrated complete regression of exercise hypertrophy after rest of five to six months. Urban examined the heart size of nine to fifteen year old boys participatng in the sports activities of the German "*Jungvolk.*" A few enlargements were observed, but since these youths were capable of work and showed no other abnormalities with exact functional tests, they were not considered pathological. Herzum (2) made an orthodiagraphic study of the heart of adolescent sportsmen among whom there was a high incidence of sizes above average which was related to the amount and duration of competitive activity. If the larger than average heart was associated with a high vital capacity, the boy also had a slower than average pulse rate and low blood pressure, and possessed a capacity above normal for the performance of work. Stine studied university boys and concluded that the normal heart does not hypertrophy because of college athletics. Keys & Friedell found no significant increase in the heart size of intercollegiate athletes. Dumitrescu & Menkes relate the heart size of Rumanian sports students to constitutional type and thoracic circumference. Meister & Kowalzig report "physiological tonogenic dilatation" and negative T waves in the resting electrocardiograms of professional wrestlers. Viciu took electrocardiograms of the participants in the Roumanian Marathon immediately after exercise and found, in the majority, changes which he interprets as indicative of myocardial anoxemia secondary to collapse of the peripheral circulation. Missal administered a stair-running test to forty normal subjects between twenty and fifty-five years of age. In none did the direction of the T wave change and in only a few did the RT

interval fall below the isoelectric line. The heart size decreases after exercise (Hannisdahl). The phenomenon is more prominent in children than adults [Ito (1)]. Liljestrand *et al.* estimate the size of the heart from bi-plane teleroentgenograms and confirm its decrease after exercise as compared with the pre-exercise volume. The change may last for hours. The values for stroke volume are the same. That this is so in spite of the smaller heart volume suggests that some extra factor, perhaps hormonal, continues to augment the degree of emptying even after the termination of work. Hynek *et al.* observed mitral configurations of the frontal view cardiac silhouettes in five per cent of 166 young adolescent Czechoslovak Sokols.

It has long been assumed that the splanchnic vessels constrict to compensate for the blood shift to the muscles during exercise. Herrick *et al.* emphasize that the constriction of a vessel *in situ* does not necessarily imply decreased blood flow. They measured the flow in a splanchnic artery and the femoral artery. Although it increased as much as three hundred per cent in the latter, there was no decrease in the superior mesenteric. Under the increase in cardiac output and the elevation of blood pressure occurring during exercise, there may be no change in the flow through the constricted vessels. On the contrary, it may increase. The blood stored in the spleen is ejected on emotional excitement, administration of epinephrine, or exercise, and the spleen decreases in volume (Grindlay and collaborators). However, splenic blood flow and volume are not reciprocal. The large cardiac output of exercise is associated with a large splenic blood flow albeit in a small spleen. After exercise, the spleen resumes its reservoir function, venous outflow subsiding abruptly, arterial inflow slowly. The rhythmic changes in volume characteristic of the spleen especially after exercise are in phase with rhythmic changes of flow in the splenic artery and probably are related to the spleen's reservoir function. Essex, Herrick, Baldes & Mann found that the marked increases in coronary flow at the onset of exercise could not be accounted for by the observed changes in blood pressure. Pulse rate was usually a much better criterion.

Silfverskiöld studied the exercise distribution of the blood pigments in the mouse. Although the parts below the level of the iliac crests contain more than one half the muscle mass of the body, the shift of blood to these regions in severe acute work

amounted to not more than ten per cent of the total. Wells, Youmans & Miller found intramuscular pressure during ordinary voluntary contraction to be lower than diastolic pressure, thus insuring a continuation of flow. Grant & Pearson observed that the increased blood flow of exercise was associated with an increase in intramuscular temperature which had a conspicuous effect, by conduction of heat, upon the temperature of the overlying skin.

Alam & Smirk have presented evidence that the retention of the metabolites of exercise causes an increase in heart rate and blood pressure by way of reflexes which arise as a result of the chemical stimulation of nerve endings in the muscles concerned. They have had the opportunity to re-confirm their observations on a subject with a cord lesion. Lankosz & Zieba studied the incidence of hypertension among some 2000 Lwow sportsmen, ranging in age from fourteen to thirty years. The systolic pressure was above 145 in from five to ten per cent of the cases, the incidence varying from sport to sport. Schneider & Collins establish a rough linear relation between venous pressure and the severity of work. Venous pressure returned to normal slowly after heavy exercise.

Respiratory patterns during movement have been studied by Basler (2). Greene & Swanson always find a period of expiratory inflation during the hyperpnea of exercise, deflation occurring with recovery. Kaufman postulates that a reciprocal action exists between respiratory and non-respiratory muscles under the control of the chemoceptor organs. Under conditions of stress, precedence is given to the respiratory reflexes.

Temperature Regulation

Nielsen made an important attack on the assumption that the elevated body temperature of exercise is caused by failure in heat regulation. The unclothed subject did constant work under room temperatures ranging from 5 to 36 degrees C. Body temperature rose to the same level with constant work in spite of drastic changes in environmental temperature and air movement. Nielsen concludes that there is no failure in heat regulation during exercise. Rather, the temperature regulating center adjusts at a higher level and maintains the body at this point during work. Hardy & Milhorat observed interesting sex differences in temperature regulation, the skin temperature of the female being higher in warm

atmospheres and lower in cold than the male. The women did not begin to sweat until the environment reached a temperature two degrees above the threshold for sweating in men and the amount of sweat was less. Ito (2) regards the ability to sweat as standing in inverse relation to the blood sugar level. Sweat production is retarded after the ingestion of glucose. Hyperglycemia has a slight inhibiting effect upon it. Studying mammals and reptiles of the American tropics, Britton & Kline (1) failed to show a uniform correspondence between the blood sugar level and thermal changes associated with stress in response to sham attacks. The inactive forms had, in general, the lowest body temperatures. Sergeyev reports that the nocturnal geckos and steppe boas move about spontaneously at great speed, even though they maintain a body temperature about ten degrees lower than the diurnal forms.

Kidney Function

Schmid found post-exercise albuminuria most frequently among winners and more often among older than young athletes. He investigated its incidence after a variety of team games. It was absent, or present only in traces in defense players, but frequent in offense players in physical activities requiring great speed. The highest incidence was in crew men, who showed red blood cells and casts, but all abnormal findings were transitory. Naeraa, studying the urinary sediments microscopically, reports red cells and casts as a frequent finding in the urine of apparently normal subjects. He observed twelve subjects in a six day bicycle race in Copenhagen and found no significant variation in red cells, but casts increased steadily during the course of the exercise. They remained hyaline in type. He does not believe that they indicate damage to the kidney. Attlee found hemoglobinuria in a school boy when he ran on a hard road but not after strenuous exercise on grass. Schmid also noted an influence of the terraine on kidney function after exercise. Rendel investigated the Donaggio reaction, much used as a test of fatigue, which is based on the fact that certain urines inhibit the passage of thionin through ammonium molybdate. Jezler examined the response of four hundred sportsmen. With increasing intensity and duration of effort, the inhibition of the Donaggio reaction increased, while training stood in inverse relation to it.

Endocrines

Ingle (1) found that the adrenals gain in weight as early as twelve hours after the beginning of stress involving continued work. Since the same hypertrophy may be produced by the administration of adrenotropic hormone, he concludes that it is mediated by this hypophyseal factor. However, Riml postulates that the adrenal stimulating material, which he demonstrates to be present in the blood of sportsmen after a 10 km. race, is formed in the muscles. He found it present also in adrenalectomized animals compelled to exercise. To test his hypothesis, Ingle (2) studied the work performance of hypophysectomized rats. Immediately after operation the ability of the muscles to contract was normal, but it rapidly decreased until it was completely lost. This occurred before the onset of any symptoms of pituitary insufficiency. There was extensive atrophy of the adrenals following hypophysectomy, while treatment with cortin partially restored the capacity for work [Ingle (3)]. Ingle, Moon & Evans observed good effects with the administration of most of the anterior hypophyseal hormones, the greatest improvement following adrenocorticotropic fraction. This compared favorably with cortin treatment. Ingle (4) finally demonstrated that the work capacity of freshly adrenalectomized rats was lost within twenty-four hours. It could be sustained by corticosterone and related compounds. Hall & Müller observed that in the absence of fatigue the spontaneous activity of normal rats was not significantly altered by cortical preparations. Britton & Kline (2) were able to arouse the sloth with their extracts of adrenal cortex, but Missiuro, Dill & Edwards found that Hartman's cortin neither produced striking effects on the resting human, nor increased the capacity for anaerobic work. However, Benetato, using the hypotensive response to histamine as a test of the suprarenal status, found a distinctly better tolerance in trained sportsmen.

Thyroidectomy was associated with a decrease in spontaneous running. However, Hall & Lindsay state that a restoration of the metabolic rate with dinitrophenol did not re-establish normal activity. Britton & Kline (3) failed to stimulate the sloth to increased activity by the administration of thyroid.

Pedersen-Bjergaard & Madsen observed a diminution of spontaneous muscular activity in castrates which could be reversed by the administration of estrogenic and androgenic substances,

implantation of crystalline testosterone propionate being the most effective of the latter. It required many times the dose effective for reproductive tract stimulation to increase muscular activity. Ingle (4) noted that estrogenic and androgenic substances and progesterone had no effect on the work performed by the adrenalectomized rat.

Milco, and Milco & Ulmeanu have endeavored to determine the influence of exercise in man upon the functional state of the endocrines as a whole, using the sero-dynamic technique of Biot-Richard.

Edwards *et al.* and Brouha, Cannon & Dill have demonstrated that the work capacity of the totally sympathectomized dog deviates little from normal. When prepared so that neither epinephrine nor sympathin are liberated, the blood sugar can still be regulated within normal limits during and after exercise. They believe this may mean, as Soskin postulated and as recently confirmed by Essex, Herrick, Baldes & Mann, that the amount of sugar in the blood is the factor which automatically regulates its release from the liver.

Emotional Stress

Britton & Kline (3) showed that emotional excitement, elevation of bodily temperature, and increased epinephrine secretion, three phenomena common to exercise, each had a marked effect upon the sloth, speeding it up more than one hundred per cent in some experiments. Muscular exercise may be used to elicit the "alarm reaction." Dalton & Selye find it at first associated with lymphocytosis, then lymphopenia, and finally, a long lasting polymorphonuclear leucocytosis. Farris (1) observed an acute, relative lymphocytosis in emotional excitement in man. This he also produced in the rat [Farris (2)]. It was much reduced after splenectomy and disappeared after adrenalectomy. Farris therefore proposes the mechanism to be one of splenic contraction through suprarenal stimulation.

Motor Ability Tests and Apparatus

There is a large literature on testing potential physical ability (Wettstone), skill (Glassow *et al.*), motor educability (Metheny), etc. From a statistical study of the age at which championships are won in a wide range of professional and amateur sports, Leh-

man shows that extraordinary proficiency comes overwhelmingly between 25 and 29, occasionally between 30 and 34, never below 25 years. However, the activities represented were largely dependent on neuromuscular skill or staying power, and not upon speed. These mature late and are relatively well maintained. Simon & Simonnet describe a new ergograph; Nielsen & Fridrichsen, a modified Krogh chair ergometer.

Casualties of Exercise

The hazards of sport and work occupy another prominent place in the literature on exercise. They include discussion of meningeal bleeding in boxing (Knoll, Stille, & Herzog), epigastralgia (Monges), allergic phenomena associated with exercise (Luckner & Mann; Grubb), muscle and joint injuries (Thorndike; Palmer; Noell; Weiss; Dumitrescu), and the development of asymmetries (Csinády & Szobonya). Katz observed that rapid stretching of the active muscle beyond its optimum length produces a break or permanently weakens parts of its contractile substance. Speidel (2) has made a ciné-photomicrographic study of injury in living muscle fibers and their repair. The muscle-tendon junction is the most vulnerable anatomical part. Maison and his associates have made direct glass electrode measurements of the changes in acidity due to muscle activity in man, to ischemic work and to fatigue. Acid changes do not seem to be the factor responsible for muscle pain. Lewis & Pochin find that pain can be elicited after all sense of position has been lost and that the muscle spindles are therefore probably unconcerned with its production. Banting *et al.* and Lougheed *et al.* have made an experimental study of the mechanism of drowning. The forced apnea is followed by a series of gasps and then violent vomiting from the distention of the stomach with aspirated water. During the preliminary brief period of struggle the blood pressure may rise to 250 or 300 mm. Hg. Electrocardiograms may be obtained for as long as twenty-five minutes after the heart sounds are inaudible.

Disturbances in function secondary to exercise have their highest incidence early in training and among champions (Cassinis). Knoll (2, 3, 4) reviews the factors predisposing to accidents, the evaluation of condition after protracted exercise, and the limits of change beyond which the effects of exercise can no longer be considered normal.

Longevity and Fitness

The influence of exercise upon longevity continues to be debated. Hartley & Llewellyn have made a careful and critical analysis of the mortality experience of oarsmen who rowed in the Oxford and Cambridge boat race between 1829 and 1928. Their data given no support to the idea that, when participated in by healthy subjects in adequate training, this vigorous exercise places any undue strain on the cardiovascular or other organs which leads to a diminution of longevity.

Hansen & McSwiney have made a survey of the widespread continental movement to stimulate interest in disciplined exercise. Cathcart reviews the contribution of physiology to "the basis of National Fitness." Woodwark sets forth the interdependence of nutrition and physical training. The year has yielded a flood of discussion in all of the scientific journals of Europe and Great Britain concerning "the dangers of physical illiteracy," "the importance of a healthy stock," "the optimal attainment of work capacity," "the benefits of exercise," "*travail et joie pour le pays et pour le roi*," the sum total of which emphasizes how much of importance in the physiology of man at work still remains a matter of empirical practice.

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PHYSIOLOGICAL PSYCHOLOGY

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The scope of the field of physiological psychology is not precisely defined. In general, it may be said that the data of experimental psychology are expressed as relationships between environmental stimulus objects and the correlated behavior of the organism, while physiology studies the functions of the component organs or organ systems of the body. Physiological psychology is then concerned with the explanation of behavioral facts in terms of the physiological mechanisms involved. Several aspects of this broad field of study are treated elsewhere in this volume (e.g., sense organs, electroencephalography).

The relationship of psychology to physiology (particularly the physiology of the nervous system) has always been a problem arousing vigorous discussion. The controversy is particularly concerned with proposed "explanations" of behavior in terms of a hypothetical neurology which lacks any direct physiological verification. Such, for example, would be Pavlov's explanation of conditioned reflexes by concepts of irradiation, concentration, and induction of excitation and inhibition in the cortex, or an explanation of memory in terms of neural traces. Skinner has presented a vigorous argument against this kind of neurological theorizing and has defended the independent status of experimental psychology. A science of behavior, he states, has no need for physiological explanations. Its laws, if valid at the level of behavior, cannot be proved wrong by neurological findings. Not only are the laws of behavior independent of neurological support, they actually impose certain limiting conditions upon a science of neurology, and in effect outline the program for such a science. The position opposite to Skinner has been most clearly defined by Pratt (1, 2), who contends that by the very nature of psychological facts, the inferred explanatory concepts must be physiological. He believes that where direct physiological knowledge is lacking, psychologists should construct, by means of the usual logic of science, the formal properties of the unknown physiological concept. In this review only the directly studied psychophysiological relations will be considered.

Two books dealing with the neurophysiological foundations of psychological functions have appeared during the past year. In a sense, these books represent the extremes of the two points of view discussed above. Rosett's *The Mechanism of Thought, Imagery and Hallucination* presents a highly speculative account of the anatomical substratum of functions such as will, symbolism, emotion, attention, and learning. Lhermitte's *Les Mécanismes du Cerveau*, on the other hand, proceeds from the verified neurophysiological data to the consideration of problems of psychological interest. After a discussion of the anatomy and physiology of the brain, he treats the topics of cerebral localization of function, conditioned reflexes, language, body images, bioelectric phenomena, and the regulatory mechanism of cortical functions.

Drive and Instinctive Behavior

General activity.—Thyroidectomy in rats produces a marked decrease in amount of spontaneous running activity in revolving cages. Hall & Lindsay have investigated the relationship between activity level and basal metabolic rate. They found that the positive correlation between these two measures was present in the thyroidectomized rats just as in normal animals. However, the restoration of the normal resting metabolic rate by administration of dinitrophenol not only failed to restore the normal activity level, but depressed it still further. They conclude, therefore, that the influence of the thyroid gland in maintaining normal activity is independent of its effect on the general bodily metabolic rate.

The observation that the frontal lobes of the cerebrum exert some kind of controlling influence over activity level has been extended in several studies. Richter & Hawkes found that unilateral, and especially bilateral, destruction of the frontal poles of the rat brain produced a definite increase in running activity. Associated with this hyperactivity was an increased food intake and decreased body weight, and a condition of increased distractibility, irritability and savageness when thwarted, which suggested a resemblance to the manic condition seen in human patients. Similar observations have been made on cats by Langworthy & Richter, and on monkeys by Messimy, and by Richter & Hines. In the last named study, a careful determination was made of the cerebral areas involved. Unilateral removal of the prefrontal cortex produced only a slight increase in activity. Sub-

sequent removal of the other prefrontal cortex was followed by a great increase. Unilateral or bilateral lesions of areas 8, 10, 11, and 12 had little or no effect, while destruction of area 9 bilaterally produced a definite increase in activity. Overactivity was produced by removal of the tip of the caudate and putamen after the previous removal of the prefrontal cortex on the same side had failed to produce an increase.

Because of its normal low level of activity, the sloth is a good animal for study in this respect. Britton & Kline (2) found that an increase in activity, measured by speed of locomotion, could be induced by injection of corticoadrenal extract, epinephrine and prostigmin, by emotional excitement, and by warming of the animal when exposed to the sun.

Hunger.—According to the generally accepted theory of the hunger drive, food deprivation leads to an organic state characterized by hunger contractions of the stomach, which in turn give rise to the sensory experience of hunger and to an intensification of spontaneous activity and of specific behavior leading to food. The ingestion of food is followed by cessation of the hunger contractions and of the drive to eat. This theory has been directly tested by several investigations and found inadequate to account for the experimental results. Tsang (3) removed the stomach from seven rats and found that the hunger drive was not significantly altered. In revolving cages the operated animals demonstrated the normal pattern of activity. During the hour before feeding they were three times as active as during the hour following feeding. In learning a fifteen unit maze, the operated animals were apparently as well motivated after one day's fasting as normal animals. By the last two of the five daily trials, however, the running time and the errors were markedly increased. The animals appeared sluggish, frequently entering a blind alley and falling asleep. Satiation seems, therefore, to result from smaller amounts of food than in normal animals.

Tsang attributed the preservation of the hunger drive after gastrectomy to the functioning of those parts of the alimentary canal adjoining the stomach, but this interpretation is rendered doubtful by the experiments of Bash (1). In a group of rats, Bash destroyed the innervation of the entire gastric region by sectioning the vagi at the level of the diaphragm and paralyzing the splanchnics with alcohol injection. This operation changed the food

behavior markedly, but did not abolish all manifestations of the hunger drive. Some of the animals refused to eat and consequently died. Those which survived ate readily and gained in weight. The normal pattern of activity before feeding time was somewhat disturbed, and the variability of the activity cycles was greater than in normal animals. On the other hand, measures of hunger drive by means of an obstruction method and by maze learning showed no difference between the operated and normal rats. In a further theoretical paper, Bash (2) accounts for the undiminished hunger drive as follows: "A thoroughly automatized conditioned response to stimulation of the distance receptors by foodstuffs, acquired in infancy and based upon an innate chemo-reflexive response to stimulation by certain tastes, is primarily responsible for the maintenance of the hunger drive in the operated animal and in the very young organism."

The factors determining hunger contractions of the stomach have been investigated in two studies by Scott, Scott & Luckhardt (1, 2). In the first experiment, blood sugar determinations were made on human subjects preceding, during, and after normal hunger periods. No variations were found, and it was concluded that the level of blood sugar bears no causal relation to the hunger periods of man. In the second experiment, they found that ingestion of alcohol markedly increased the intensity of hunger sensations in human subjects without increasing the height of the stomach contractions as measured by the usual balloon technique.

Further evidence on this point is provided by Morgan who showed that insulin hunger does not depend upon increased gastric motility. He denervated the stomach in a group of rats to eliminate the effect of insulin upon stomach contractions, and found that the effect of insulin upon the amount eaten did not differ in operated animals from normal animals fed on the customary diet. With a high sucrose diet, insulin increased eating in vagotomized rats and decreased it in normal rats. This result is explained in terms of changes in blood sugar level.

Richter and his associates have carried forward their extensive program of studies of appetite as a function of bodily needs. Rats were given opportunity for self selection of food from several available containers, and the amount of each food or fluid which was ingested was determined daily. By this method it has been demonstrated that normal rats have definite appetites for protein,

carbohydrate, sodium, calcium, phosphorus, potassium, and the vitamins. Their choice of diet, when unrestricted, was such as to be conducive to normal growth and reproduction. Richter & Barelare (1) showed that during pregnancy and lactation, female rats consumed more than normal amounts of protein and fat, while carbohydrate intake remained unchanged. There was also an increased demand for sodium chloride, sodium phosphate, and particularly for calcium lactate. Richter & Eckert found that adrenalectomized rats, which as the result of excessive loss of sodium chloride in the urine usually die within five to fifteen days, would ingest large amounts of salt sufficient to keep them free of deficiency symptoms. Adrenalectomy also produced an increased appetite for sodium lactate and sodium chloride, but not for chlorides of iron, magnesium, calcium, aluminum, potassium, or ammonium. When such rats were offered free choice of six mineral solutions, the relative proportion of the increased intake of the different ions was practically the same as is found in normal blood serum. Not only did adrenalectomized rats have an increased appetite for salt, but also a lowered taste threshold for salt (Richter, 2). This result indicates that adrenalectomized rats ingest more salt, not because they learn that salt relieves their deficiency discomforts, but because of chemical changes in the taste mechanisms in the oral cavity, giving rise to an enhanced salt discrimination. The possibility is suggested that taste thresholds may serve as a delicate index of bodily deficiencies in human patients (Richter & MacLean).

Rats on a diet deficient in vitamin B showed an aversion for carbohydrate and protein and a craving for fat. Given access to yeast, they consumed it eagerly and thus corrected the deficiency (Richter, Holt, Barelare & Hawkes). A further analysis of the components of vitamin B in relation to appetite has been carried out by Richter & Barelare (2). Six groups of rats on a basal diet deficient in vitamin B were given access to one or several of the component vitamins. Rats given thiamin ate normal amounts of sucrose, stopped drinking olive oil, but refused to eat protein (casein). Rats given riboflavin displayed an increased appetite for casein and survived longer than any of the other groups. Rats given nicotinic acid showed little change from those on complete vitamin B deficiency. Rats given factor W showed a constant and normal olive oil intake.

Jukes has reported that chickens fail to select a diet containing proper food constituents when given free choice. She found that both normal chickens and those fed a diet deficient in vitamin G showed no preference between two diets of which one contained vitamin G. However, Jukes was careful to make both diets identical in taste, texture and appearance. If Richter's contention that changes in food preference depend upon changes in the taste mechanism, the results of Jukes are not out of harmony.

Thirst.—Richter (1) has collected observations by himself and others on the maximum water intake of rats, cats, dogs, monkeys, and human beings. He found that the intake of normal animals was a function of surface area rather than of body weight, and hence must be a function of metabolism. On the other hand, the maximum water intake of animals with diabetes insipidus was found to be a function of body weight rather than of body surface. This limit might be determined by the maximum capacity of the kidney or by the maximum capacity of all the cellular spaces of the body, both of which would be functions of body weight.

Adolph has shown that there is a precise correlation between the water deficit of the body and the amount of water ingested. This was true both for normal dogs and for dogs with fistula of the esophagus which prevented the ingested water from reaching the stomach. The rate of drinking (gulps per minute) was nearly constant, decreasing slightly during any one drinking period. The rate of drinking, however, was proportional to the amount of bodily water deficit. Further study of the time factors in drinking was carried out by Bellows with fistulous dogs. Such a dog with a constant water deficit would sham drink approximately the same amount of water when offered it at hourly intervals. With shorter intervals, the amount sham drunk was generally less; with longer intervals, the amount did not increase. If a connecting tube was fitted in the esophagus so that the water drunk reached the stomach, the amount ingested was similarly proportional to the deficit, but the dog would refuse to drink one hour later or at subsequent periods. Bellows points out that the satisfaction of thirst is not a single process such as wetting the mucous membranes of the mouth, but a series of at least two supplementary and consecutive processes. Passage of an excessive amount of water through the mouth and pharynx confers immediate but temporary satisfaction of thirst. Drinking is inhibited when the ingested water enters the

gut below the upper esophagus. The short period of temporary satisfaction secured by the passage of water through the mouth and pharynx is superseded by the delayed process of permanent satisfaction operating lower in the gut.

Bellows & Van Wagenen (2) have attempted to secure critical evidence on the theory that thirst depends upon local sensations from the mouth and throat. They prepared three groups of dogs: in the first the gustatory sense was abolished by division of the glossopharyngeal nerves and chordae tympani bilaterally; in the second all sensations except taste were abolished from the buccal cavity by division of the trigeminal nerves bilaterally; in the third the olfactory sense was abolished by resection of the olfactory tracts. Water drinking in normal amounts or in the excessive amounts of diabetes insipidus was not abolished or altered by any of these procedures. In a further study of the mechanism of diabetes insipidus, Bellows & Van Wagenen (1) attempted to show that this condition results basically from the polydipsia, and that the polyuria is a secondary phenomenon. The pathological thirst could not therefore be accounted for by the theory of local sensations from the mouth, since there was no dehydration of the body. They proposed an alternative theory of thirst, in which the hypothalamic center is conceived to operate in a manner similar to the respiratory center to produce thirst which is then relieved by instinctive drinking.

Sex.—A comprehensive review of the recent literature on sex drive and behavior is presented by Stone in a chapter of the second edition of the book *Sex and Internal Secretions*. Stone discusses the role of the endocrines, the nervous system and of development in the mechanism of the sex drive, the measurement of the intensity of sex drive and of factors affecting it, and the interrelation of various measures of sex drive with themselves and with measures of other drives and interests.

A quantitative description of sexual behavior in the female guinea pig has been presented by Young, Dempsey, Hagquist & Boling. Continuous day and night observations of 617 female guinea pigs throughout a total of 2102 heat periods was carried out. The period of sexual receptivity was clearly recognizable by noting the straightening of the back and the elevation of the pudenda when the female was stroked on the back or mounted by a male. The period of heat varied in length from one to more than

thirty hours, averaging eight to nine hours. Entirely different from the copulatory response, but usually associated with it, was the male-like mounting activity by the female. This behavior was shown most commonly about the beginning of heat. Further papers in the series from this laboratory deal with the mechanism of artificial induction and control of heat by hormone injections (Young, Dempsey, Myers & Hagquist; Boling, Young & Dempsey; Collins, Boling, Dempsey & Young).

Beach (2) has noted several instances of reversal of sex behavior in rats. One sexually normal male rat was observed to display typically feminine copulatory response to the sexual advances of a more aggressive male. Seven sterilized virgin females were observed to respond to passive males by the adoption of the masculine sex pattern. They returned immediately to the feminine behavior pattern when the male assumed a sexually aggressive attitude. The effect of thymus extract on the sexual behavior of the female rat has been studied by Bruner & Cunningham. Seven mature animals were given injections of thymocrescin for a period of five weeks. In comparison with a group of litter mate control animals which received injections of normal saline solution, the experimental animals evoked fewer copulatory responses from males with which they were placed, and when mounted, made fewer copulatory or combative responses and more indifferent responses. The characteristic shivering and quick darting of the female in heat was observed in only two of the twenty-one mating observations. Ball found that injection of estrin in normal female rats produced a reduction in receptive sexual behavior.

The relation of sexual and general personality traits is a complex one which can be approached from many different angles. Anderson has found a significant relation between sexual drive in rats and emotionality as measured in four different situations. Rats with strong sex drive showed much less emotionality than rats with weak sex drive. Anderson believes that this antagonism may be found to be an expression of reciprocal relations among the thyroid, pituitary and gonad mechanisms. Benedek & Rubenstein have analyzed the material of psychoanalytic records of patients during the phases of the sex cycle and found that heterosexual tendencies were correlated with estrin activity and passive receptive and narcissistic attitudes with progesterone activity.

The recent synthetic production of testosterone propionate has

made possible the study of male hormone effects upon sexual drive. Sollenberger & Hamilton have shown that injections of testosterone produce an increase in sex activity in adult guinea pigs which had been castrated pre-pubertally. Hamilton has demonstrated precocious masculine behavior in young chickens following administration of testosterone. Injections in female canaries were observed to induce the typical male song (Leonard), and other masculine characteristics such as courtship behavior and dominance in the pecking order (Shoemaker). Miller, Hubert & Hamilton have described the psychological changes resulting from administration of testosterone to clinical cases of adult castration, hypogonadism, senile prostatic hypertrophy and psychic impotence. Marked increases in erectile capacity of the penis and in the strength of sex urge were observed. Bize & Moricard reported marked changes in personality in young boys with hypogenitalism or adiposity when injections of testosterone were carried out over a period of months. There was an impression of increased strength and intellectual curiosity, and an increased aggressiveness, shown by a detachment from the family group and a greater tendency to assertiveness. Sollenberger has found a definite relationship between the amount of male sex hormone in the urine of adolescent boys and their maturity of interests and attitudes and their social relations.

In his presidential address before the Eastern Psychological Association, Lashley (1) reviewed some of the theoretical and experimental problems of instinct, using reproductive behavior as an illustration. He distinguished instinct from reflex in terms of the patterned character of the effective stimulus for the former, and proposed that all cases of motivation be treated, not as general drives or disturbances of organic equilibrium, but as partial excitation of very specific sensori-motor mechanisms. The action of hormones or of sensory impulses from the viscera can then be understood as the activation of some central neural mechanism maintaining excitability or activity. Dempsey & Rioch have undertaken to localize the brain regions necessary for sexual behavior in the female guinea pig. Transection experiments demonstrated that the fundamental central mechanism is located caudal to the anterior margin of the mammillary bodies and rostral to the intercollicular level. The evidence suggests that the site of action of estrin and progesterone is on this center. Further experiments

localized an afferent pathway in the posterior columns of the cord which decussates at some point below the posterior corpora quadrigemina and runs through the roof of the mesencephalon. Dempsey found that normal mating behavior in the guinea pig was not abolished by brain lesions in the septal and preoptic regions, in the pretectal area, or after section of the pituitary stalk. Lesions destroying the posterior corpora quadrigemina abolished mating behavior but did not interfere with ovulation. Papanicolaou & Seward showed that heat could be induced by hormone injections in the guinea pig after double hysterectomy, indicating the direct action of the hormones on the nervous system. The action of sex hormones on the central nervous system has also been investigated by Vanderplank by the use of conditioned swimming movements in the fish *Leuciscus leuciscus*. Estrin was found to inhibit the conditioned response, while progesterone had no direct effect but terminated the inhibition resulting from estrin.

Sleep.—Clinical and experimental data have provided a large body of evidence that the hypothalamic region is important in the sleep mechanism, but the nature of the hypothalamic control is far from clear. Ranson found that bilateral destruction of the lateral hypothalamic area in monkeys was followed by profound somnolence. This is the area which, on electrical stimulation, produces combined sympathetic and somatic excitation, and emotional expression is possible only when the area is intact. In view of the fact that the descending pathways from the sympathetic nuclei of the hypothalamus traverse this area, Ranson believes that the somnolence may be attributed to the elimination of the normal efferent discharge of the hypothalamic centers. The hypothalamus might therefore more properly be called a "waking" center than a "sleep" center.

This conception receives independent support from an investigation by Serota, utilizing a technique for the measurement of thermal changes in localized regions of the cat's brain. In the conscious and in the anesthetized animal the basal brain regions were found to be warmer than the cortex. Emotional states such as fear, rage, or anticipation of food increased the relative temperature of the hypothalamus. During sleep the relative hypothalamic temperature was decreased and stabilized; on awakening, it rose earlier and farther than that of the cortex, caudate nucleus or Ammon's horn. These changes were not due to altered blood flow,

because only an insignificant drop in blood flow during sleep was recorded with the Gibbs thermoelectric recorder. Serota concluded that the lowered hypothalamic temperature was an expression of decreased nerve cell metabolism.

Changes in cerebral circulation during sleep have been studied by Nygard, who recorded brain volume with a tambour placed over the skull opening in patients with temporal decompression or frontal craniotomy. During sleep there was an increased volume and a more pronounced pulse, accompanied by a slower heart rate and a slight decrease in blood pressure. Since he found that the circulatory changes followed rather than preceded the onset of sleep, the author does not consider a circulation theory of sleep tenable.

Schnedorf & Ivy have reexamined the evidence for the hypnotoxin theory of sleep. When eight cubic centimeters of cerebrospinal fluid was withdrawn from a normal dog and replaced by an equal quantity of cerebrospinal fluid from dogs kept awake for seven to sixteen days, there was a sleep-like reaction in nine of twenty instances. Only four of twenty-four control dogs which received fluid from normal dogs showed any comparable effect. The authors found that the increase in intracranial pressure could not account for the results, but their analysis of the injected fluid gave no clue to the specific chemical mechanism involved.

Emotion

The experimental study of emotion has been surveyed by Lund in a book which gives particular attention to the cardiovascular, respiratory, gastrointestinal, sexual, metabolic, and skin changes induced by emotional situations. One of the least regular bodily responses in emotion is the pulse rate, and widely divergent effects have been reported by different experimenters. Beebe-Center & Stevens have suggested that the cardiac acceleration often observed in emotion is perhaps a secondary effect of muscular exertion. They recorded heart rate electrically in a gun-shy dog subjected to pistol shots, and found a marked correlation between cardiac acceleration and violence of overt muscular movements. A similar suggestion might be derived from the findings of Freeman & Simpson with the galvanic skin response. This reaction, often correlated with emotion, was found to be directly proportional to the degree of muscular tension induced in human subjects

by pressing both feet against a calibrated scale resistance. Britton & Kline (1), however, found no uniform correspondence between general somatic expression and glycemic or thermal changes in a series of tropical animals studied. Brown & Van Gelder have carried out a series of physiological measurements on students in a less artificial emotional situation than is usually studied in the laboratory. They found that before important examinations, college students showed increased systolic blood pressure, increased pulse and respiratory rates, increased blood sugar, and in some cases, glycosuria. No change occurred in erythrocyte or leucocyte counts or in diastolic blood pressure. Ziegler & Cash found an inconstant effect of emotional reactions upon skin temperature in a series of psychiatric patients, but Mittelmann & Wolff recorded a consistently large fall in skin temperature during emotional states induced in patients by recalling or probing their real-life problems.

The localization of brain centers involved in emotional experience and expression continues to be a controversial problem. In his studies of decorticate guinea pigs, K. U. Smith (2) found that there was an over-reaction to tactual stimuli, which might be interpreted as emotional in character. On the other hand, reflex immobility, which has sometimes been interpreted as a type of fear reaction, was lost rather than exaggerated. The role of the hypothalamus in emotion has been investigated by Masserman. Destruction of one side of the hypothalamus in cats produced, twenty or more hours after operation, a condition of apathy and torpor alternating with variable periods of restlessness and manifestations of emotional irritability. Complete bilateral destruction of the hypothalamus resulted in persistent stupor, which gave place to pseudaffective manifestations of rage when the animal was annoyed or restrained. Compared with the normal cat, the rage reaction was variable and disorganized and was not accompanied by attempts at escape or defense.

Chief support for the theory that in emotion the thalamic centers are released from cortical inhibition has been derived from clinical studies of patients with the thalamic syndrome. Kozol, among others in recent years, has questioned this interpretation. He reported a case of thalamic syndrome displaying typical symptoms of dysesthesia and overreaction to sensory stimuli. Following surgical excision of a porencephalic cyst and associated scar tissue,

there was marked improvement with complete abolition of the dysesthesia. Kozol favors an irritation theory rather than a release theory, since an operation which extended the neural damage brought relief of the syndrome. Marquis & Williams were also led to question the release theory of the thalamic syndrome. Patients who had marked sensory overreaction to cutaneous stimuli demonstrated no exaggeration of sympathetic (vasomotor) reactions to those stimuli.

Lashley (2) has challenged the evidence for the hypothesis that the thalamus is the essential neural center for emotion. Accepting the fact that the thalamus (hypothalamus) mediates some of the patterns of overt emotional response, he finds no support for the conception that the thalamus adds the affective or emotional character to experienced sensations. The affective changes resulting from thalamic lesions are restricted to certain somesthetic sensations and cannot be interpreted as a general change in affectivity. The changes correlate definitely with the special properties of conduction, summation, and irradiation of this group of sensory processes and not at all with a specific locus in the thalamus. The symptoms of thalamic lesions are concerned with the intensity, duration, and localization of sensations and are, therefore, not relevant to the problem of affect. Rioch also questions the concept of localization of normal emotion in the thalamus and hypothalamus. Emotional expression in the decorticate cats cannot be considered normal because of the rapidity with which the reaction subsides when the stimulus is terminated, and because succeeding reactions are not affected by the preceding ones.

Cerebral Mechanisms of Sensory Functions

Visual functions.—It is known from previous work that a habit based on the discrimination between two lights of different intensity can be performed by the rat after complete destruction of the visual cortex (area striata), or after destruction of the anterior corpora quadrigemina. Ghiselli (1) found that an operation which combined destruction of the visual cortex with large lesions of the anterior corpora quadrigemina was followed by no greater effects than either lesion alone. In addition to the lateral geniculate nucleus and the anterior corpus quadrigeminum, the only other termination of fibers from the optic tract is in the nucleus of the transverse peduncular tract, the large celled nucleus, and the pre-

tectal nucleus. Earlier work has shown that the nucleus of the transverse peduncular tract is not sufficient for brightness discrimination, and Ghiselli & Brown (1) undertook to determine the part played by the remaining two nuclei. Bilateral destruction of either the pretectal nucleus or of the large celled nucleus did not prevent the formation of the brightness habit. The results indicated that destruction of any one of the several nuclei of termination of the optic tract does not destroy brightness discrimination. The authors point out, however, that there is not a complete equipotentiality among the centers. Removal of the geniculocortical system produces an amnesia for the brightness discrimination habit acquired prior to operation, while destruction of any of the midbrain nuclei produces no impairment of the retention. They conclude that in the normal rat the striate cortex mediates brightness discrimination, but after removal of the cortex, the function is presumably mediated vicariously by one or all of the subcortical centers.

Although cortical lesions do not impair the ability of rats to learn a simple light discrimination, Ghiselli (2) has shown that they do have an effect upon the rate of learning a habit requiring the discrimination of four successive pairs of brightnesses. The degree of retardation in twenty-six animals was directly proportional to the size of the cortical area destroyed, but was independent of the locus of the lesion. These results are similar to Lashley's findings with the maze habit. They support the conclusion that the retardation cannot be explained on the basis of a sensory deficit, but must be due to the disturbance of some non-sensory integrating function of the cortex in which all areas are equipotential. A similar interpretation has been advanced by Hebb (1, 2) to explain the effect of cerebral lesions upon the ability of the rat to locate food in an open field situation, but his evidence is not conclusive. Hebb (3) has also shown that the removal of the visual cortex does not impair the transposition of the brightness discrimination habit. Rats were trained to choose one (e.g., the brighter) of two light intensities, and were subsequently presented with a choice between the positive light and another still brighter light. Operated animals, like normal animals, chose the new brightest light, indicating that they were responding to relative rather than absolute intensity.

Ten Cate has confirmed the earlier finding that after bilateral

removal of the area striata in dogs, conditioned responses can still be established to a change in light intensity. He found further that these conditioned responses were not disturbed by additional bilateral lesions in the cortex bordering on the original extirpation, or in the frontal lobes. It is concluded that the response to light which survives removal of the occipital lobes is not mediated vicariously by the remaining cortex, but must be subcortical.

In contrast with brightness discrimination, the discrimination of visual pattern or form depends upon the integrity of at least a portion of the visual cortex. In the lower mammals, however, a rudimentary pattern vision may persist after complete removal of the visual cortex. K. U. Smith (1) found that one of three cats was able, after ablation of the occipital lobes, to discriminate a horizontal luminous rectangle from a vertical rectangle of the same area and brightness. Whether this performance involved true pattern discrimination or merely a discrimination of difference in brightness when the animal looked at some particular spatial point was not determined. Kennedy has examined the effect of cortical lesions on the ability of cats to discriminate absolute and relative speed of movement of two visual patterns equated in size and brightness. Complete bilateral removal of the area striata in seven cats interfered so markedly with their performance that threshold determinations were impossible, but evidence was secured that movement discrimination was possible under conditions of very high speed with simplified patterns. There is at present no evidence of more than brightness vision in the monkey after removal of the occipital lobes. Unilateral occipital lobectomy does not impair fine color discrimination (Maison, Grether & Settlage), and removal of one occipital lobe plus varying amounts of the macular (lateral occipital) cortex of the other lobe produces no residual impairment of color or form vision, or of more complex tasks involving vision (Settlage).

In view of the almost complete loss of pattern vision in the discrimination test situation, it is significant to note that the nystagmus response to a moving pattern in the visual field is very little impaired by complete destruction of the visual cortex in animals. Smith & Bojar have reviewed the extensive literature on optic nystagmus in normal and operated animals. Quantitative study of the threshold conditions for elicitation of optic nystagmus has been undertaken by Smith & Warkentin in cats after bilateral

occipital lobectomy. With white lines moving across a black field, the width of the lines need not be significantly greater for operated than for normal animals (visual angle of 0.5 minute). Confirming previous results, they found that the operated animals did not respond to single moving lines, or to widely spaced lines. It is concluded that "optic pursuit movements related to single or isolated patterns in the visual field are mediated cortically, while similar responses to closely spaced patterns on the retina may be determined subcortically in the absence of the visual cortex. In the latter case, the pursuit responses to a series of adjacent striations depend upon summation of impulses in subcortical centers."

Disturbances of visually determined behavior resulting from lesions of the cerebrum outside the area striata have been the subject of two investigations. Kennard found that unilateral ablation of area 8 in the frontal lobe of the monkey led to a characteristic failure of response to visual stimuli. The defect could not be differentiated from true hemianopsia except that it was transient, and that bilateral operation did not result in blindness. The monkeys ignored objects in the contralateral homonymous visual field and also used the contralateral hand less often and less effectively in retrieving seen objects. Kluver & Bucy have described symptoms of visual agnosia or "psychic blindness" in a rhesus monkey after bilateral extirpation of the temporal lobes. The operation apparently did not produce any serious visual field defect or any impairment of ability to discriminate differences in brightness, size, shape, distance, or position of visual stimuli. There semed to be a complete loss, however, of the ability to recognize and detect the meaning of objects on the basis of optical criteria alone. The animal would pick up all objects indiscriminately and convey them to the mouth. Only after the oral examination would the nonedible objects be rejected. There was also a marked emotional apathy after the operation, which only slowly and partially disappeared in the course of months.

Auditory functions.—A rare case of cortical deafness in man has been reported by Clark & Russell. Symmetrical vascular lesions in the external capsules isolated the insular cortex and the submerged cortex of the upper surface of the middle third of the superior temporal convolutions in both hemispheres. There was complete degeneration of the medial geniculate nuclei. Comparable experimental destruction of the temporal lobes in animals is known,

however, not to produce any severe impairment of discrimination of intensity or pitch of auditory stimuli. Girden (1, 2) has investigated the cerebral areas necessary for the localization of sounds by dogs. The animals were trained by a motor conditioning procedure to flex their leg when a sound stimulus came from the right, but not when the same sound came from the left. Complete transection of the corpus callosum or extirpation of one entire hemisphere did not abolish correct differential response, although after both temporal lobes were extirpated the dogs were unable to localize sound. Pennington found that bilateral destruction of the auditory cortex in rats resulted in an amnesia for a habit of auditory localization which had been learned before operation. In distinction from the results on dogs, however, the rats were able to learn the auditory localization habit after operation.

Ades, Mettler & Culler have studied the hearing loss in dogs after small localized lesions in the medial geniculate nucleus. Their evidence indicates that the spiral organ (of Corti) is projected spatially on the nucleus, with the high frequencies in the dorsal section and the low frequencies in the ventral region. Since different frequencies traverse the geniculate nucleus by separate pathways, it follows that pitch discrimination occurs prior to this point (at the cochlea).

Somesthetic functions.—The cerebral mechanism of a habit based on kinesthesis has been investigated in rats by Ghiselli & Brown (2). The animals were trained to choose between two inclined runways which differed in the angle of inclination. A group of forty-one rats with various small subcortical lesions were compared with normal animals. The structures which appeared to be of functional importance in the kinesthetic habit were the medial lemniscus, the ventral nucleus (pars externa) of the thalamus, and the globus pallidus. D. E. Smith devised a somesthetic discrimination test for rats in which the animals were forced to choose between two pathways one of which was covered with sandpaper and the other was smoothly varnished. He found that large lesions in the frontal region of the cortex produced an impairment of the habit. Small frontal lesions or lesions of any size in other parts of the cortex were not followed by loss.

Parallel studies of the cortical localization of somesthetic functions in monkey, chimpanzee, and man have been reported by Ruch, Fulton & German. A striking result was the finding that

in all subjects, relatively large lesions of the parietal lobe did not result in complete and permanent anesthesia. A progressive corticalization of function is reflected in the degree of impairment following lesions of the postcentral gyrus and the posterior parietal lobules. In the monkey no disturbance of weight discrimination ability was produced; in the chimpanzee there was a deficit which disappeared with retraining; in man a definite, if small, permanent deficit was observed.

Recovery after cerebral lesions.—A discussion of the factors limiting recovery of function following lesions of the central nervous system has been presented by Lashley (3). In some cases there is an immediate spontaneous reorganization without relearning, which produces an abnormal but functionally useful adjustment. Explanation of such recovery is difficult in simple neurological terms. Cases of long delayed restitution of function fall into two classes: spontaneous and learned. The former are usually ascribed to the disappearance of the effects of diaschisis. Lashley finds no specific evidence for diaschisis and attributes the delayed spontaneous recovery to the functional dependence of one behavior system upon some other more fundamental organization. Delayed recovery which depends upon relearning is called vicarious functioning. The neural tissue involved in relearning a destroyed function is in every case, however, normally concerned either with the same or with related functions. Lashley reviews the experimental evidence for the conception that the degree of recovery depends upon the total mass of remaining functional cerebral tissue. This relationship is not attributed to the elimination of the several diverse functions of the different areas removed, but to a reduction of some more general cortical activity such as has been characterized as vigilance.

A marked degree of recovery was noted by Ruch, Fulton & German in somesthetic functions following parietal lobe lesions. Retraining was found to be a very important factor in this recovery. Several facts suggest that the improvement was specific to the particular testing situation, and the authors infer that the basis of improvement lies in a more effective utilization of residual sensory cues. Settlage noted a great recovery of certain functions in monkeys following partial occipital lobe ablation. The animals were tested in a series of seven situations in which they had to pull in the correct one of two or more strings in order to obtain food.

The strings were arranged in different patterns, for example, crossed, converging, etc. Although there was no final loss in capacity to perform these problems, there was a severe temporary impairment following operation. The existence of hemianopsia and macular scotomas, and the persistence of preoperative habits of bodily orientation and visual fixation, were postulated as explanation of the immediate loss of function. The monkeys apparently saw only a portion of each string pattern. Recovery was presumed to depend upon learning to use perceived objects to infer the existence of a larger situation, and developing the capacity to respond on the basis of less than normal visual cues. Harlow has tested the effect of visual experience during the recovery interval upon the degree of restitution of this function. Monkeys which were kept in darkness for ten days following unilateral occipital lobectomy were definitely inferior to monkeys which had normal daylight cage experience during that time. The interval in darkness had no effect itself upon the performance of normal monkeys. Harlow also found that there is a high degree of specificity in the recovery process; reorganization of the visual field following practice in one situation did not guarantee successful solution of highly similar situations.

Previous clinical and experimental study has indicated that recovery is better in young than in older individuals. Tsang (1) compared the maze learning performance of rats which had been subjected to partial decortication at different ages. He found that the effects were more severe following the operation in adults. Lesions of less than ten per cent of the cortex, if made on adult rats, produced as much loss in maze learning ability as lesions of forty per cent of the cortex in infant rats. In a subsequent investigation Tsang (2) found that although removal of the visual cortex in adult rats abolished all pattern discrimination, the equivalent destruction in infants left some residual ability. Four of the forty infant rats were able to discriminate the direction of lines in the visual field at about one thirtieth of normal acuity. Beach (1) found similar effects of cortical lesions on instinctive maternal behavior in rats. Destruction of forty per cent of the cortex in adult animals practically abolished maternal behavior, while similar lesions inflicted at birth seemed to have no significant effect upon later caring for the young.

Cerebral Mechanisms of Learning and Intelligence

The experimental study of the effect of extirpation of various areas of the brain upon adaptive behavior has been reviewed recently by Jacobsen. He stresses the newer knowledge of the relation of cortical and subcortical mechanisms, and the development in the higher mammals of specialized structural differentiations for mediating complicated behavioral adjustments.

Conditioned responses.—Previous work has established the general conclusion that a conditioned response depends upon the integrity of the cortical sensory area corresponding to the particular conditioned stimulus, although a primitive kind of conditioning is possible in dogs after complete removal of the cortex. The cortical motor center for the conditioned response has not been found to be essential for successful performance, but Allen has challenged the general validity of this statement. Extirpation of the excitable motor cortex in dogs prevented the formation of a conditioned leg retraction response based on shock, and abolished such a conditioned response which had been established before operation. The conditioned stimulus in these experiments was olfactory. Rey found no cortical localization in rats of a conditioned response which has no definite specifiable conditioned stimulus. He trained the animals to leap from a grill, whenever they were placed on it, in order to avoid subsequent electric shock. Large destructions of the cortex produced a temporary impairment of this response, but the effect was independent of the locus of the destruction.

Most of the treatments of the neural basis of conditioning and learning are purely speculative and hypothetical. Direct physiological study of the nervous system has dealt almost entirely with the very brief effects of stimulation and not with the long-lasting effects which must underlie permanent learning. A few studies, however, suggest the possibility of a more direct approach. Shurrager & Culler have reported that a form of conditioned response can be obtained in the semitendinosus muscle of the spinal dog. Further study of this phenomenon may throw important light on the neural mechanism of conditioning. Culler has also reported a study of direct cortical stimulation of a conditioned response. Dogs were trained to withdraw their foreleg in response to a tone stimulus presented in combination with a shock to the paw. The cerebral hemispheres were then exposed, and exploratory electrical stimulation of the cortex contralateral to the trained leg revealed

a small spot in the anterior ectosylvian gyrus from which the conditioned leg response could be elicited. This spot was not in the primary auditory area or in the somesthetic sensory area; it was also not the motor point for leg flexion. Dogs tested prior to any conditioning showed no response to stimulation of the spot, and the response could be evoked in trained dogs only as long as the conditioned tone stimulus was capable of evoking the response. When the conditioned response was extinguished by unreinforced repetitions, the response to electrical stimulation of the cortical spot also disappeared. When the response to tone was reconditioned, the response was again evokable by cortical stimulation.

Maze learning.—The cerebral mechanism of maze learning by rats has been the subject of much interest because of the finding that the various areas of the cortex are equipotential, and that the degree of impairment of the maze performance is proportional to the amount of cortex destroyed irrespective of its locus. Brown & Ghiselli found this same equipotentiality to hold for subcortical destruction. Forty-five rats with discrete electrolytic lesions in various regions of the subcortical brain structures were trained in an eighteen-unit maze. As a group the animals were inferior to normals, and those with lesions in the region of the thalamus showed the greatest impairment. However, no single subcortical structure was found to be essential for maze performance.

Several studies have undertaken to analyze the nature of the impairment of maze performance following cortical destruction. Ghiselli & Brown (3) found that the relative difficulty of the various units of the maze was reversed for operated rats as compared with normals. Ericksen (2) also found a differential effect upon types of errors. Operated animals were less able to learn those maze turns which were opposite in direction to the food box, and those turns near the end of the maze which were opposite in direction to the final turn (anticipatory errors). Operated animals were also less susceptible to interference errors in the transfer from one maze to another similar one. Hu confirmed the previously observed fact that cerebral lesions reduce the capacity for retention of learning over a forty day interval, as well as the capacity for initial learning. When a new maze learning task was interpolated between the original learning and the retention test, the normal and the operated rats showed the same degree of disruptive effect. Hu also concludes that the factor of cerebral lesion is a

much more important variable than is time or interpolated learning in determining the degree of retention, but this conclusion is obviously limited to the specific conditions of his experiment. Ericksen (1) found that for operated rats, original learning was more difficult than transfer to a similar maze, and relearning the same maze was least difficult.

Frontal lobes and intelligent behavior.—The experimental study of animals has shown that the frontal lobes are not an essential mechanism for adaptive learned behavior with the exception of certain performances, such as delayed reaction, which involve a choice response in the absence of differential sensory cues. Finan found, however, that bilateral removal of the prefrontal areas in monkeys did not abolish successful performance in two tests of temporal discrimination. He concluded that the deficit following frontal lobe ablation is not the loss of ability to respond in the absence of differential sensory cues, but must be interpreted in some other way.

The clinical literature on the psychological changes following destruction or extirpation of the frontal lobe is not within the province of this review. Nearly all of the studies agree that if the lesion is restricted to one hemisphere, even the dominant one, no serious effect on personality or intelligence is observed [Lidz; Hebb (4)]. However, Brickner and Halstead found that there was an observable syndrome follow ng unilateral lesions when careful methods of examination were employed. The nature of the psychological syndrome is most completely presented by Rylander in his book on personality changes after operations on the frontal lobes.

Amentia.—Present day research trends in the field of human physical and mental deficiency have been reviewed by Humphreys, with particular reference to genetic, chemical, and physiological factors. Norman has made a microscopic study of the cortex of the brains of thirty normal and thirty mentally defective individuals. No difference in depth of cortex or in average nerve cell count was found, but the distribution of neuronic cytons throughout the middle portion of the supragranular cortex was significantly less uniform in defectives than in normals. Several other studies suggest the possibility of the correlation of physiological or constitutional deficiency with amentia. Gordon & Norman found that in a group of 336 institutionalized mental defectives, abnormal neurological signs were more frequent in the lower grade patients.

Jervis has isolated a type of amentia associated with excretion in the urine of phenylpyruvic acid. The condition appears to be a genetic one, and is characterized by a definite physical constitution and extrapyramidal neurological signs. Mental retardation has also been found to be associated with rickets (Hallerman), congenital heart disease (Ross), and low basal metabolic rate (Hinton; Dispensa).

Physiological Factors in Mental Efficiency

A comprehensive review of recent investigations of the effect of alterations in the internal environment upon psychological performance has been published by Shock. He deals with such factors as anoxia, increased air pressure, changes in acid-base equilibrium, drugs, and blood sugar level.

Sleep loss.—The effect of varying periods of sleep loss has been studied by Bunch, Frerichs & Licklider. Using white rats, they found that the ability to learn a difficult water maze was above normal for animals kept in a condition of apparent wakefulness for 8, 16, 24, and 48 hours. No significant differences between the four wakeful groups appeared.

Drugs.—Alcohol is known to have a detrimental effect upon practically all functions studied, but the extent to which different types of performance are affected is still an open question. Mead found that an experimental dose of 30 cc. pure ethyl alcohol in 150 cc. total volume decreased the percentage of improvement in an artificial language test but had no effect upon a conditioned finger withdrawal. The author concluded that alcohol exhibited a more deleterious effect on higher mental performance than on simpler reflex functioning. Brun found that after administration to rabbits of 0.2 cc. to 18 cc. of 96% alcohol, there was a progressive increase of the vestibular chronaxie, proportional to the dose of alcohol, followed by a progressive decrease to the normal value before the states of alcoholic narcosis had worn off.

Caffeine has been shown to have a stimulating effect upon color sensitivity and performance on certain psychomotor tasks. Thornton, Holck & Smith found that 300 mg. of caffeine sodium benzoate produced an increase in unsteadiness, tapping, handgrip, and speed of reaction as shown by two tests. On the third test, simple auditory reaction time with a preparatory interval, the results were doubtful. Kravkov obtained an increase of as much

as forty per cent in color sensitivity to reddish orange and green light after a caffeine dose of 100 mg.

Short & Johnson have compared the reactions of the human body to tobacco smoke and to epinephrine. In five subjects, measurements of skin and oral temperature, blood pressure and pulse rate changes, and blood sugar and cholesterol fluctuations were made during a period of one and a half hours while cigarettes were being smoked, and later after the injection of one cc. of 1:1000 epinephrine solution. There was a remarkable parallelism in the bodily effects of the two treatments, which is interpreted as confirmation of the view that the characteristic physiological effects of smoking are due to the increased output of epinephrine.

Several clinical investigations have reported observations on the psychological effects of amphetamine (benzedrine). Schilder has pointed out that the effects of amphetamine, the most common being a feeling of tenseness with disappearance of fatigue and inhibitions, are due not alone to the structure of the drug but to the structure of the personality as well. He considers the drug helpful in bringing forward important material in the course of analytic treatment. Reifenstein & Davidoff found that the effects were characterized by variability, uncertainty, and unpredictability. Cutts & Jasper administered doses of amphetamine sulfate (20 mg. for six days) to twelve behavior problem children with abnormal electroencephalograms. Those patients who were distinguished by a prominent six cycle rhythm in the electroencephalogram showed marked improvement with amphetamine.

Barmack found that 10 mg. of amphetamine sulfate retarded a drop in the rate of adding six-place numbers for two hours, and also delayed the development of boredom, strain, irritation, fatigue, and inattentiveness. The number of errors made did not appear to be affected. Carl & Turner, studying the effects of 10, 20, and 30 mg. doses of amphetamine upon performance in a comprehensive psychometric examination, found that this drug appeared to have relatively little effect upon accuracy but increased speed. From the Bernreuter personality inventory, an optimism-pessimism scale, and twenty-four self-rating scales given during the course of the examination, amphetamine appeared to produce a definite heightening of mood, a fairly generalized optimism and interest, together with an increased willingness to work for extended periods of time (Turner & Carl). The authors stated that

the optimal dosage for a given individual could be determined only by further experimentation. Thornton, Holck & Smith reported the improvement of scores on three reaction time tests, three tapping tests, handgrip and steadiness tests to be greater with 20 mg. of amphetamine than with 300 mg. of caffeine sodium benzoate. The stimulating effect of amphetamine on general activity is confirmed by Searle & Brown in their experiments on white rats. When the drug was administered every fourth day to a group of fifteen white rats, the spontaneous activity was markedly increased during the first hour after injection, falling off to normal in about four hours. Since there was a compensating decrease during the rest of the twenty-four hour period the total activity on amphetamine days did not differ significantly from that on control days. Hence amphetamine caused, not an absolute increase of the energy expression, but rather a redistribution of it. Doses of 3 mg. per kg., subcutaneously injected, produced a greater increase in activity than did doses of 1.5 mg. or 4.5 mg. (Brown & Searle). Wentink found that the rate of conditioning in four rats was increased 142 per cent by injection of 0.5 mg. of amphetamine.

A summary of the results of quantitative experiments using amphetamine indicates, in general, a loss of fatigue, an increase in feelings of well-being, an increase in general activity, and an increase in the rate of work with little effect upon the accuracy of work.

Anesthesia.—A series of experiments on the recovery and induction sequences in anesthesia have been carried out by Cornsweet (1, 2). Albino rats were subjected to varying amounts of ether, cyclopropane, nitrous oxide, or ethyl alcohol until a complete state of quiescence was reached. The loss of motor function was observed to be caudo-cephalad and recovery cephalo-caudad in every case. Though the rapidity of the effects produced varied with the anesthetizing agent employed, the temporal sequence was the same. The author points out that the caudo-cephalad induction is apparently contrary to medical theory of anesthetization on human subjects where the order is supposedly cerebrum, spinal cord, and medulla. Deshaies has described the sequence of post-operative awakening from anesthesia in sixty-five human subjects. He also found that motor activity returned in a cephalo-caudal sequence. The anesthetics used were ether, Schleich's mixture, chloroform, nitrous oxide, and ethyl chloride. Related

observations have been made by Cohen on the return of cognitive conscious functions after convulsions induced with metrazol. The characteristic sequence of recovery was sensory processes, attention, recognition of objects, correct use of objects, and memory.

Diet.—Biel has investigated the effects in rats of severe inanition during the first few weeks of life. A group of thirty-two animals were put on a reduced diet immediately after birth by restricting the time allowed for nursing. This was continued for twenty-five days until weaning. The rats were retarded in physical development, and showed less ability in learning a maze. The effects of inanition were not permanent however. Tested at thirty-six to ninety days of age, the rats reached normal performance, and the conclusion is drawn that in inanition, development proceeds at a slower rate but to the same final stage. Poe, Poe & Muenzinger found that impairment in maze learning resulted from diets deficient in vitamin-B complex or in vitamin B_1, but much less from diets deficient in vitamin B_2(G). In his studies of food storing behavior in rats, Wolfe noted that such behavior was much more prominent in animals which were fed a quantitatively inadequate diet than in normal animals. Jakway found that the addition of yeast to a vitamin free basal diet increased the spontaneous activity of rats.

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